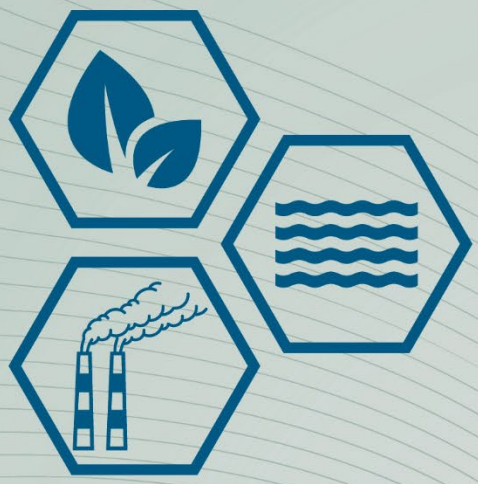

Toxicological Profile for Copper

October 2024

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(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, intermediate, and chronic health effects; and

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
October 2024	Final toxicological profile released
April 2022	Draft for public comment toxicological profile released
September 2004	Final toxicological profile released
October 1990	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Copper (Cu), a naturally occurring chemical element and essential mineral, is a reddish heavy metal that is found in rock, soil, sediment, and water, and at low levels in air. The Earth's crust is the primary natural source of copper, with an average copper concentration of 50 ppm (Henckens and Worrell 2020). Natural background concentrations of copper in soils have been reported to range between 2 and 50 ppm (Oorts 2012). Copper levels in soils are dependent on the physical structure, conditions, and natural and industrial history of the area. Local concentrations may be elevated above background levels in agricultural and industrial areas. Average concentrations of 2,545 and 397 ppm were measured in soils and sediments, respectively, at various monitoring sites across the U.S. between 2020 and 2022 (Oorts 2012; WQP 2022). In a geological survey reported in 1984, the geometric mean concentration of copper in samples of soils and other surficial materials from across the United States was 17 ppm, with an estimated arithmetic mean of 25 ppm (USGS 1984). Copper also occurs naturally in all plants and animals and is found in some foods and nutritional supplements. In the United States, the geometric mean serum copper level for all adults (≥18 years old) in the 2015–2016 National Health and Nutrition Examination Survey (NHANES) was 1,146.6 µg/L (18.1 µmol/L). According to the 2020 survey titled *What we eat in America*, 18% of all individuals ≥20 years old reported using supplements containing copper (USDA 2020). For males ≥20 years old, the mean nutrient intake of copper from foods was 1.3 mg/day and the intake from foods plus supplements was 1.5 mg/day. For females ≥20 years old, the mean nutrient intake of copper from foods was 1.1 mg/day and the intake from foods plus supplements was 1.3 mg/day (USDA 2020).

Copper is an essential micronutrient necessary to human and animal health. For adult men and women, the National Academies Institute of Medicine's Recommended Dietary Allowance (RDA) and Tolerable Upper Intake Levels (ULs) of copper are 900 and 10,000 µg/day (9 and 10 mg/day), respectively; however, these values vary for children and for lactating and pregnant females. Copper is required for many physiological functions, but excess intake of copper can result in toxicity and may also decrease the absorption of other essential minerals such as zinc. Excess copper exposure can result from external environmental sources such as copper contamination in drinking water. Some health conditions in humans also disturb copper homeostasis in the body.

Copper is mined in the United States and abroad and is also recovered from scrap, which makes up a significant portion of the U.S. copper supply. It is an important commercial metal due to its various

properties including corrosion resistance, durability, ductility, malleability, antimicrobial behavior, and electrical and thermal conductivity. Copper and copper compounds are used in several industries including construction, electrical, transportation, and smelting processes. Specific uses of both copper and its compounds include plumbing, electrical wiring, electrical devices, cookware, animal feed, fertilizers, wood preservatives, roofing, and marine antifouling paints (Henckens and Worrell 2020). Due to their antimicrobial properties, copper compounds are used as antimicrobial agents in drinking water treatments, and copper alloys are used in heating, ventilation, and air conditioning. Copper is also found in ointments and creams as well as multivitamins and dietary supplements. Copper intrauterine devices (IUDs) are a popular form of birth control. Copper nanoparticles, which can be formed naturally or through chemical synthesis, have a variety of uses including as an antibiotic, antimicrobial, and anti-fungal agent in plastics, coatings, textiles, and pharmaceuticals. The toxicity of copper nanoparticles is distinct from the toxicity of ionic copper due to their presence in the metallic state and their particle size. This is described in further detail in Section 2.21.

The general public is exposed to copper daily from many sources including air, food, water, and products containing copper. Humans are most likely to ingest copper in its salt form but can also be exposed to other forms via inhalation and, to a lesser extent, dermal exposure. In ambient air sampled between 2020 and 2022, the mean copper concentration across 10–13 U.S. monitoring stations ranged from 0.0182 to 0.0238 μg/m^3 (EPA 2022a). Concentrations in drinking water can vary widely from ≤5 to 53,200 μg/L (see Section 5.5.2). In 0.03% of principal aquifers in the United States sampled by the U.S. Geological Survey (USGS) from 1991 to 2010 and 0.06% of domestic wells sampled by USGS from 1991 to 2004, copper was found at concentrations greater than the U.S. Environmental Protection Agency (EPA) action level (see Section 5.5.2). The EPA action level for dissolved copper in drinking water is 1.3 mg/L. Since the implementation of the EPA's Lead and Copper Rule in 1991, action level exceedances have decreased by over 90% (EPA 2019, 2020b). Copper-contaminated water may have a light blue or blue-green color with a metallic, bitter taste. Soluble copper has been detected in a wide range of food products including fruits, meats, breads, processed foods, dairy, bottled water, and juices, among others. Copper has also been measured in blood, urine, hair, nails, and human breastmilk.

1.2 SUMMARY OF HEALTH EFFECTS

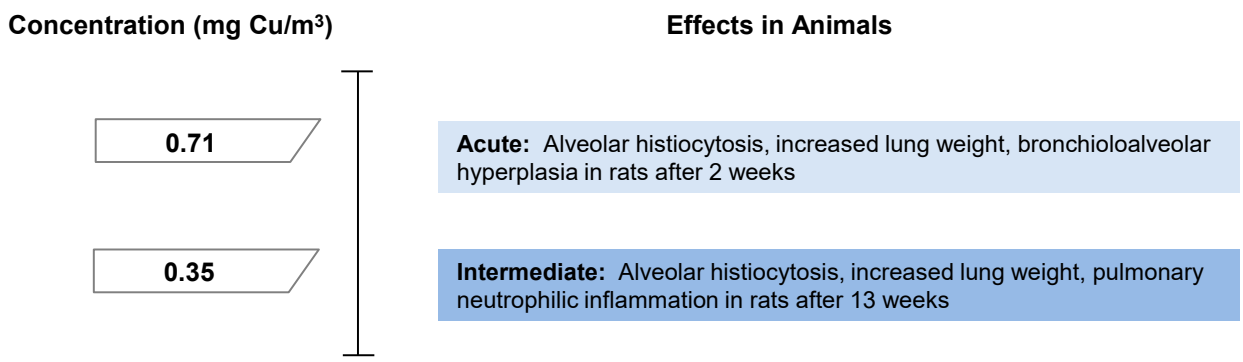
Information on the toxicity of copper and copper compounds comes primarily from oral studies in both humans and animals exposed to copper sulfate. The vast majority of human studies are case reports of accidental or intentional ingestion of copper compounds; however, several human controlled oral exposure studies are also available, primarily evaluating gastrointestinal and hepatic effects. There were

very few inhalation and dermal studies of copper compounds in humans. Most of the animal studies used oral administration; a small number of inhalation studies were also identified, but no primary dermal studies were identified.

Figures 1-1 and 1-2 summarize the health effects observed in human and animal inhalation and oral studies, respectively. As the figures indicate, the most sensitive endpoints for copper toxicity in humans and animals following oral exposure are the gastrointestinal tract and the liver. The most sensitive endpoint for inhaled copper in humans and animals is the respiratory tract. A systematic review of these endpoints resulted in the following hazard identification conclusions:

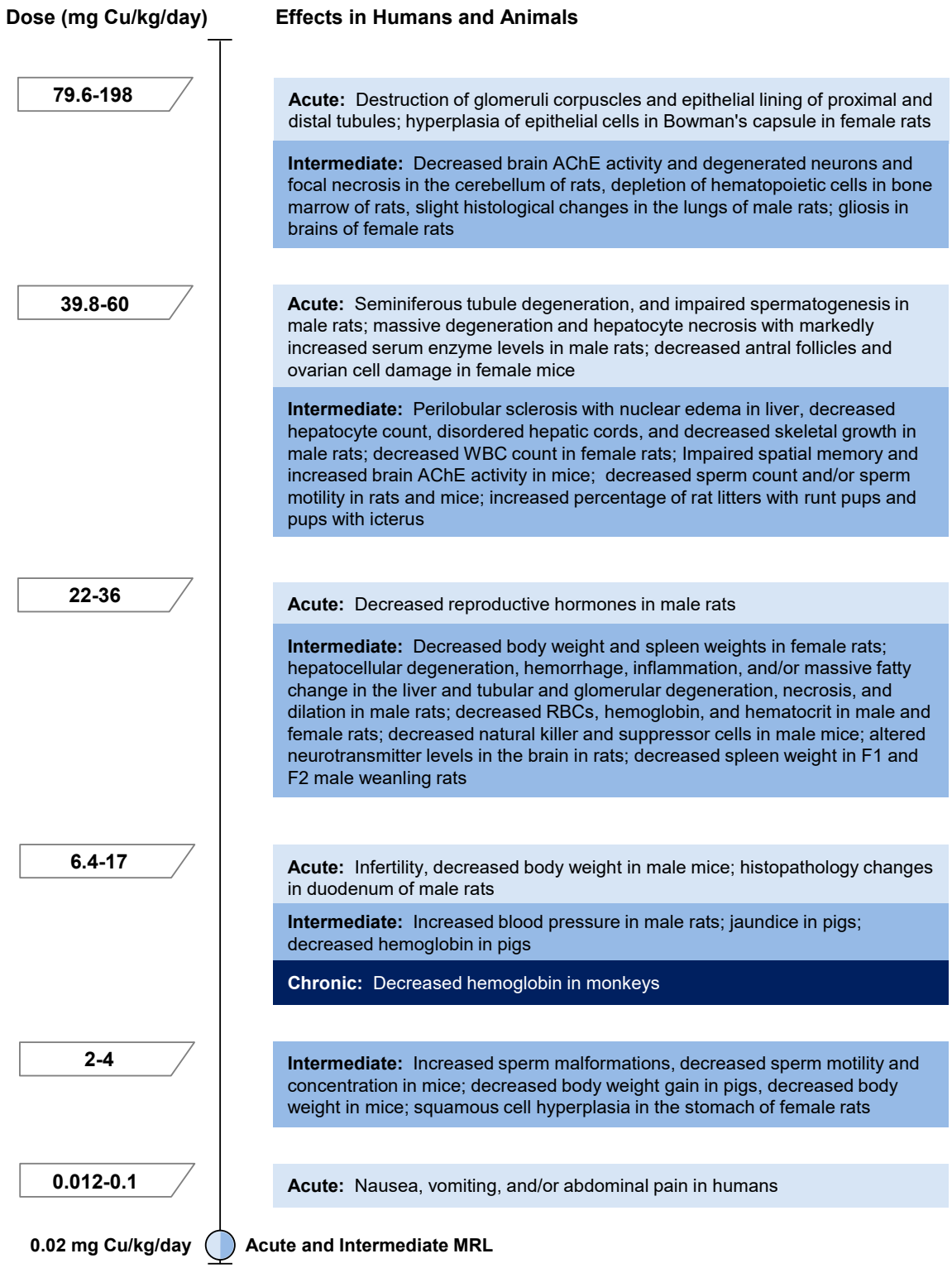
- Gastrointestinal effects are a known health effect for humans following oral exposure.
- Respiratory effects are a presumed health effect for humans following inhalation exposure.
- Hepatic effects are a presumed health effect for humans following oral exposure.

Figure 1-1. Health Effects Found in Humans and Animals* Following Inhalation Exposure to Copper



*All effects listed were observed in animals, unless otherwise specified.

Figure 1-2. Health Effects Found in Humans and Animals* Following Oral Exposure to Copper



*All effects listed were observed in animals, unless otherwise specified.

Gastrointestinal Effects. Numerous acute-duration controlled-exposure studies (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001; Pizarro et al. 1999, 2001) have documented gastrointestinal upset, primarily nausea, vomiting, and abdominal pain in humans from oral exposure to copper. A study in humans identified a dose-response relationship between ingestion of drinking water with elevated copper levels and gastrointestinal symptoms (Pizarro et al. 1999). Other gastrointestinal effects induced by copper in controlled-exposure studies included delayed gastric emptying (Araya et al. 2003a) and increased gastric permeability (Gotteland et al. 2001), both of which were independent of the gastrointestinal symptoms. Case reports of intentional or accidental ingestion of copper, and health investigations of communities with elevated copper in drinking water, provide support for the gastrointestinal effects in humans. Acute-duration oral exposure of shrews to copper also induced vomiting (Yamamoto et al. 2004). Studies of laboratory rats and mice indicate that oral copper exposure results in histopathological changes in the stomach or forestomach (squamous cell hyperplasia; hyperkeratosis), duodenum (loss of enterocyte arrangement, necrotic debris), and/or intestine (ulceration) after acute and intermediate durations (Chung et al. 2009; Husain et al. 2021; Kadammattil et al. 2018; NTP 1993).

Respiratory Effects. Occupational health studies have reported respiratory symptoms in workers exposed to copper dusts (Askergren and Mellgren 1975; Suciu et al. 1981). In addition, epidemiological studies of respiratory effects in workers exposed by inhalation have reported increased respiratory symptoms, as well as associations between copper exposure and diminished pulmonary function as measured by spirometry (Fouad and Ramadan 2022; Mourad and El-Sherif 2022; Saadiani et al. 2023). One of these studies reported a higher prevalence of radiological infiltrates in chest x-rays of copper smelter workers compared with unexposed administrative workers (Fouad and Ramadan 2022). In well-conducted acute- and intermediate-duration experiments in rats, exposure to copper sulfate pentahydrate or dicopper oxide particles induced increased lung weight, bronchoalveolar lavage fluid (BALF) changes, and histopathological changes in the respiratory tract (alveolar histiocytosis, bronchioloalveolar hyperplasia, acute neutrophilic inflammation in the lungs, and nasal olfactory epithelial degeneration) (Poland et al. 2022). Most studies that evaluated the respiratory tract in animals exposed orally to copper did not report effects, but Draper et al. (2023) reported histological changes (including thickened interalveolar septa and epithelial desquamation) in the lungs of rats exposed to a high dose (161.5 mg Cu/kg/day) of copper sulfate pentahydrate by daily gavage for 28 days.

Hepatic Effects. Human case studies reported increases in liver enzymes (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST]), liver impairment, jaundice, centrilobular necrosis, and

hepatomegaly following exposure to very high doses of copper substances (Ahasan et al. 1994; Akintonwa et al. 1989; Chuttani et al. 1965; Du and Mou 2019; Gamakaranage et al. 2011; Gunay et al. 2006; Lamont and Duflou 1988; Lubica et al. 2017; O'Donohue et al. 1993). Controlled-exposure studies, where humans were exposed to lower levels of copper in drinking water or capsules, found no alterations or indications of damage to the liver, including in studies conducted in infants (Olivares et al. 1998) and adults (O'Connor et al. 2003; Pratt et al. 1985). Evidence of hepatotoxicity resulting from excess copper exposure primarily comes from laboratory animal experiments, and most of these studies examined rats. Liver effects reported in rats exposed orally for acute or intermediate durations included elevated serum levels of liver enzymes or cholesterol and histopathological changes including degeneration, necrosis, parenchymal cell hypertrophy, chronic hepatitis, edema, hepatocellular hemorrhage, fatty change, chronic inflammation, inflammatory cell infiltration, and bile retention (Alhusaini et al. 2018a, 2018b; Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980; Haywood and Comerford 1980; Haywood and Loughran 1985; Kumar et al. 2015, 2016a, 2016b; NTP 1993; Patwa and Flora 2020; Rana and Kumar 1980; Sakhaee et al. 2012; Seven et al. 2018; Sugawara et al. 1995; Temiz et al. 2021; Yu et al. 2021a). Similar hepatic changes were noted after intermediate-duration oral exposure in mice (Dab et al. 2023; Liu et al. 2020a, 2020b, 2021a, 2021b; Sakhaee et al. 2014). Jaundice was seen in pigs after intermediate-duration oral exposure (Suttle and Mills 1966).

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of copper. IARC lists copper 8-hydroxyquinoline as not classifiable as to its carcinogenicity in humans due to lack of cancer studies in humans and animals (IARC 1987). Neither the National Toxicology Program (NTP) nor the EPA has evaluated the carcinogenicity of copper (IRIS 1988; NTP 2021).

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, following acute- and intermediate-duration inhalation exposure, the respiratory tract is the most sensitive target of copper toxicity. The inhalation database was inadequate for the derivation of inhalation MRLs for any duration of exposure. The gastrointestinal tract, liver, kidney, and neurological system appear to be sensitive targets of oral copper toxicity, as shown in Figure 1-4. The oral database was adequate for the derivation of an acute-duration oral MRL for copper. The intermediate-duration oral database provided support for the adoption of the acute-duration oral MRL. There were insufficient data for the derivation of a chronic-duration oral MRL for copper. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Copper – Inhalation

Available data indicate that the respiratory tract is the most sensitive target of copper inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.

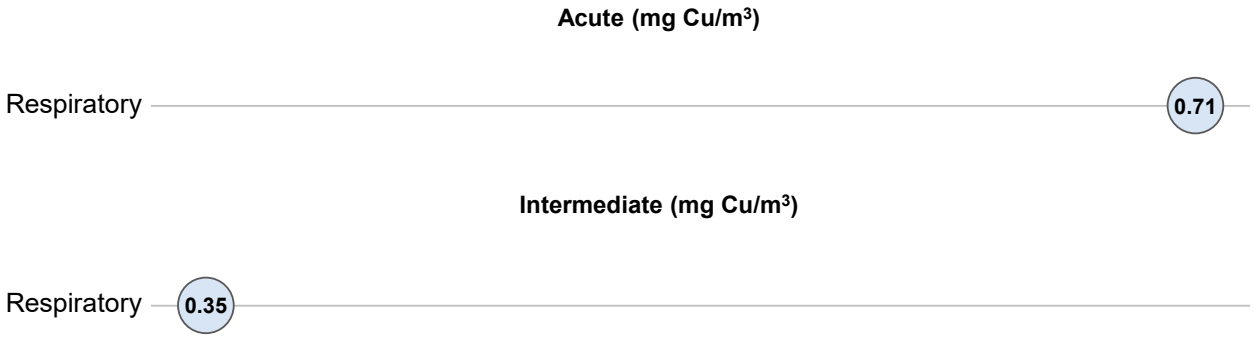


Figure 1-4. Summary of Sensitive Targets of Copper – Oral

Available data indicate that the gastrointestinal, hepatic, renal, and neurological systems are the most sensitive targets of copper oral exposure.

Numbers in triangles and circles are the lowest LOAELs among health effect in humans and animals, respectively.

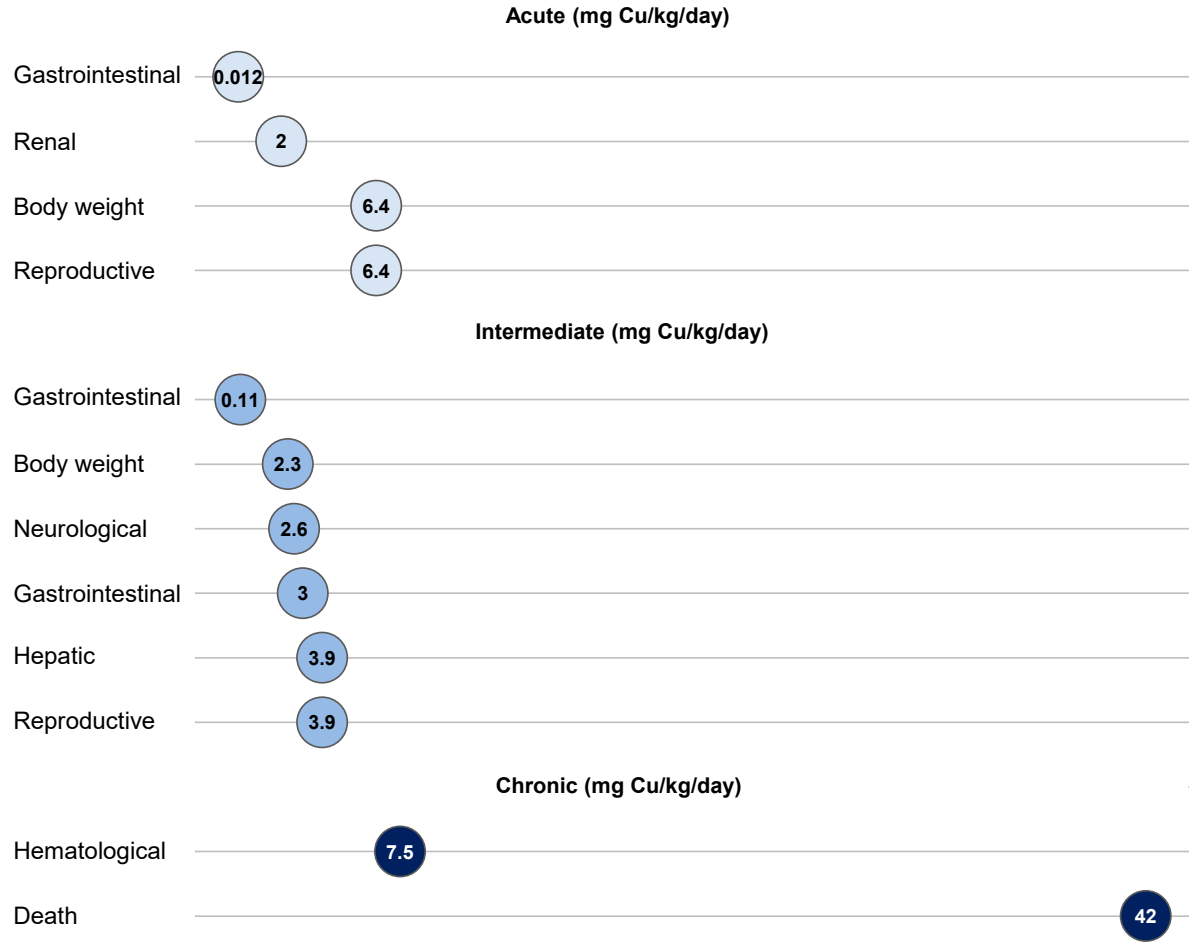


Table 1-1. Minimal Risk Levels (MRLs) for Copper[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**No inhalation MRLs were derived for any duration.**						
Oral	Acute	**0.02 mg Cu/kg/day**[b]	Gastrointestinal effects	$BMDL_{10}$	0.055 mg Cu/kg/day	UF: 3	Pizarro et al. 1999
	Intermediate	**0.02 mg Cu/kg/day**[c]	Gastrointestinal effects	$BMDL_{10}$	0.055 mg Cu/kg/day	UF: 3	Pizarro et al. 1999
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]The acute-duration oral MRL of 0.02 mg Cu/kg/day reflects the intake of administered copper in addition to dietary background. It is intended to protect against gastrointestinal effects in people who receive adequate copper intake from diet and/or supplements. People who have copper deficiency may be given therapeutic doses at or above the MRL.
[c]The acute-duration oral MRL was adopted for the intermediate-duration oral MRL.

$BMDL_{10}$ = benchmark dose lower confidence limit associated with 10% extra risk; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 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.

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to copper, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to copper was also conducted; the results of this review are presented in Appendix C.

Animal and human inhalation studies are presented in Table 2-1 and Figure 2-2, and animal and human oral studies are presented in Table 2-2 and Figure 2-3.

Levels of significant exposure (LSEs) 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. Effects have been classified into "less serious LOAELs" or "serious LOAELs (SLOAELs)." "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 endpoint 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 endpoints. 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 the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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. The RDA for adult humans is 0.9 mg Cu/day (IOM 2006), and typical diets in the United States contain adequate copper to meet this requirement (NIH 2022). The normal serum copper level in human adults is 10–25 μmol/L (64–160 μg/dL) (IOM 2006). In the human body, copper levels are carefully regulated by transporter proteins that control its absorption, distribution, and excretion (see Chapter 3).

Copper deficiency is relatively rare in humans, but has occurred in infants given formula or cow's milk deficient in copper (IOM 2006). In addition, intake of high levels of zinc or iron may interfere with copper absorption and lead to deficiencies (IOM 2006). Finally, Menke's disease, caused by a mutation in the Menkes P-type ATPase gene, results in impaired copper absorption and copper deficiency (IOM 2006). Copper deficiency is associated with anemia, leukopenia, neutropenia, and osteoporosis (IOM 2006). Several diseases in which copper accumulates in the body have also been identified in humans. These diseases, characterized by severe liver toxicity, are described briefly in Section 2.4, Hepatic.

This toxicological profile is focused on the effects of excess copper exposure from exogenous sources (i.e., not resulting from impaired excretion of copper). Studies of excess copper effects in humans include controlled human studies, epidemiological studies, occupational and community health investigations, and case reports/case series. Controlled human exposure studies are included in the LSE tables for the appropriate exposure routes. Epidemiological studies that met inclusion criteria (see Appendix C, Section C.2.2) are summarized in tables and/or text within each health effect subsection below.

Occupational and community health investigations and case reports/case series are described in text in the corresponding health effect subsection.

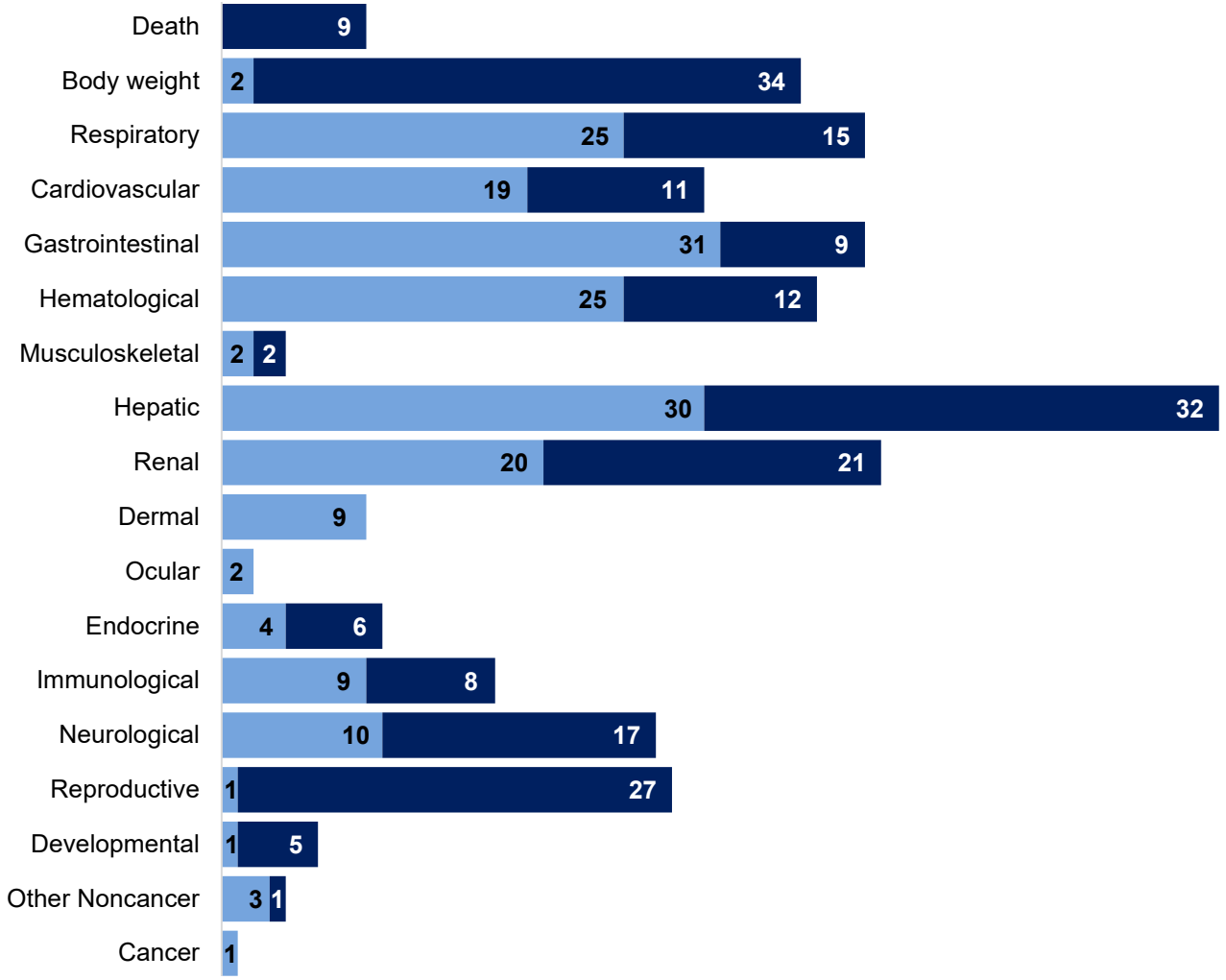
The database of animal studies investigating health effects of copper is large, and the quality of the studies varies widely. Only studies that met inclusion criteria (see Appendix C, Section C.2.2) are discussed in Chapter 2. It is important to note that the majority of animal studies did not report the concentration of copper in the controls' diet or drinking water. As an essential element, copper is typically a constituent of laboratory animal feed, and may also occur in tap water. For the purpose of hazard identification, it is assumed that modern studies provided adequate copper intake in controls to prevent effects of deficiency. Similarly, since copper absorption in the gastrointestinal tract is reduced when zinc intake is high, it is assumed that studies included herein provided adequate, but not excessive, zinc intake for control and exposed animals.

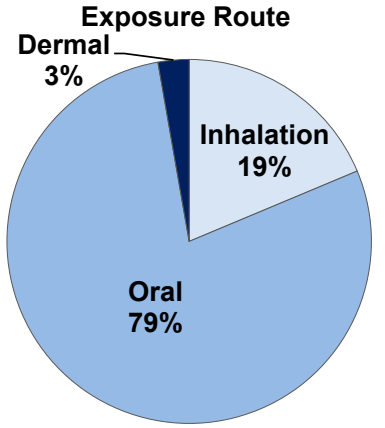
Information in this toxicological profile on health effects of copper comes from 88 human and 94 animal studies that met inclusion criteria. Relevant health effects data for copper are shown in Figure 2-1. As indicated in the figure, the largest numbers of human studies examined gastrointestinal and hepatic effects; the vast majority of these were case reports or case series. Most of the animal studies administered copper orally. The animal studies primarily examined body weight, hepatic, and reproductive effects. Human studies suggest that gastrointestinal effects are a sensitive target of oral exposure to copper, while animal studies suggest that hepatic effects are a sensitive target of oral exposure and respiratory effects are a sensitive target of inhalation exposure.

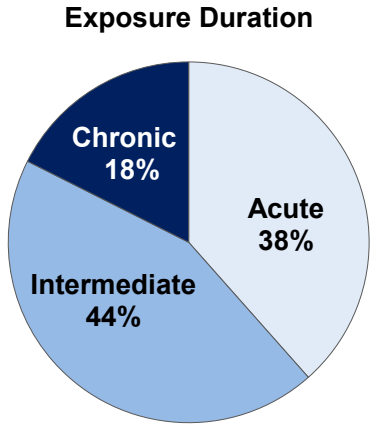
- **Gastrointestinal endpoints:** Gastrointestinal toxicity is a known health effect in humans exposed orally to copper based on a high level of evidence in humans and a high level of evidence in animals.
- **Respiratory endpoints:** Respiratory toxicity is a presumed health effect in humans based on a low level of evidence in humans and a high level of evidence in animals exposed by inhalation.
- **Hepatic endpoints:** Hepatic system toxicity is a presumed health effect in humans based on a high level of evidence in animals.

Figure 2-1. Overview of the Number of Studies Examining Copper Health Effects*

Most studies examined the potential gastrointestinal and hepatic effects of copper.
More studies have evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint).







*Includes studies discussed in Chapter 2. A total of 161 studies (including those finding no effect) have examined toxicity. Studies may have examined more than one endpoint.

Table 2-1. Levels of Significant Exposure to Copper – Inhalation (mg Cu/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Poland et al. 2022									**Dicopper oxide**
1	Rat (Crl:CD (SD)) 5 M, 5 F	6 hours/day 5 days/week 2 weeks (WB)	0, 0.18, 0.71, 1.78, 8.9	LE, CS, BW, FI, GN, OW, HP	Bd wt	8.9			
					Resp	0.71	1.78		Alveolar histiocytosis in both sexes; increased absolute and relative lung weight in females
					Hepatic	8.9			
					Renal	8.9			
Poland et al. 2022									**Copper sulfate pentahydrate**
2	Rat (Crl:CD (SD)) 5 M, 5 F	6 hours/day 5 days/week 2 weeks (WB)	0, 0.18, 0.71, 1.78, 8.9	LE, CS, BW, FI, GN, OW, HP	Resp	0.18	0.71		Alveolar histiocytosis in both sexes, bronchioloalveolar hyperplasia in males
					Hepatic	8.9			
					Renal	8.9			
INTERMEDIATE EXPOSURE									
Poland et al. 2022									**Dicopper oxide**
3	Rat (Crl:CD (SD)) 10–20 M, 10–20 F	6 hours/day 5 days/week 4 weeks (WB)	0, 0.18, 0.35, 0.7, 1.76	LE, CS, BW, FI, HE, GN, OW, HP	Bd wt	1.76			
					Resp	0.18	0.35		Increased absolute and relative lung weight, neutrophilic inflammation in lungs, alveolar histiocytosis, increased LDH and total protein in BALF
					Hemato	1.76			
					Hepatic	1.76			
					Renal	1.76			
					Neuro	1.76			
Johansson et al. 1983									**Copper chloride**
4	Rabbit (NS) 8 M	1 month 5 days/week 6 hours/day	0, 0.6	IX	Resp	0.6			
					Immuno	0.6			

Table 2-1. Levels of Significant Exposure to Copper – Inhalation (mg Cu/m^3)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Johansson et al. 1984									**Copper chloride**
5	Rabbit (NS) 8 M	4-6 weeks 5 days/week 6 hours/day	0, 0.6	GN, HP	Resp	0.6			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BALF = bronchoalveolar lavage fluid; Bd wt or BW = body weight; CS = clinical signs; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; IX = immune function; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Resp = respiratory; WB = whole body

Figure 2-2. Levels of Significant Exposure to Copper – Inhalation
Acute (≤14 days)

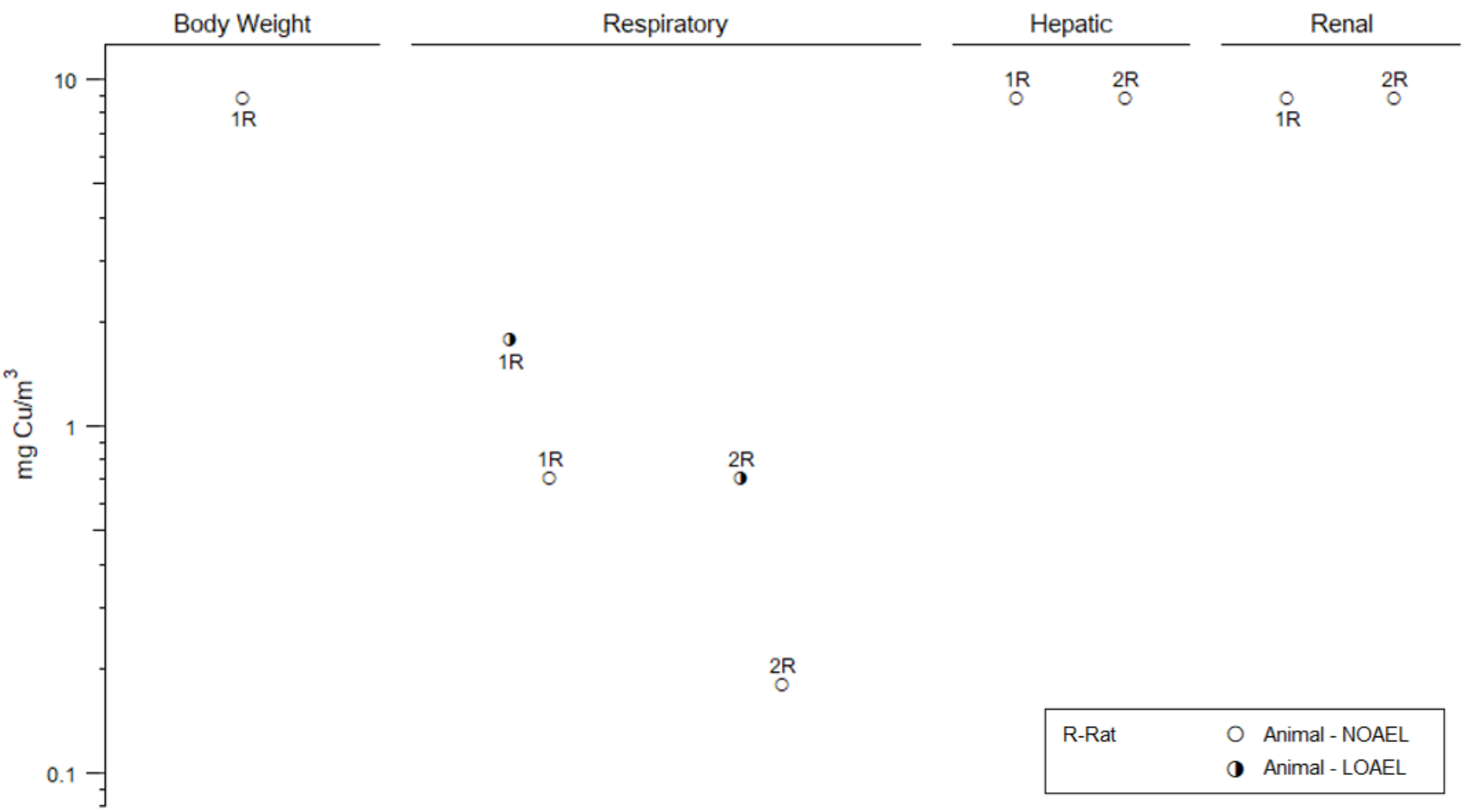


Figure 2-2. Levels of Significant Exposure to Copper – Inhalation
Intermediate (15–364 days)

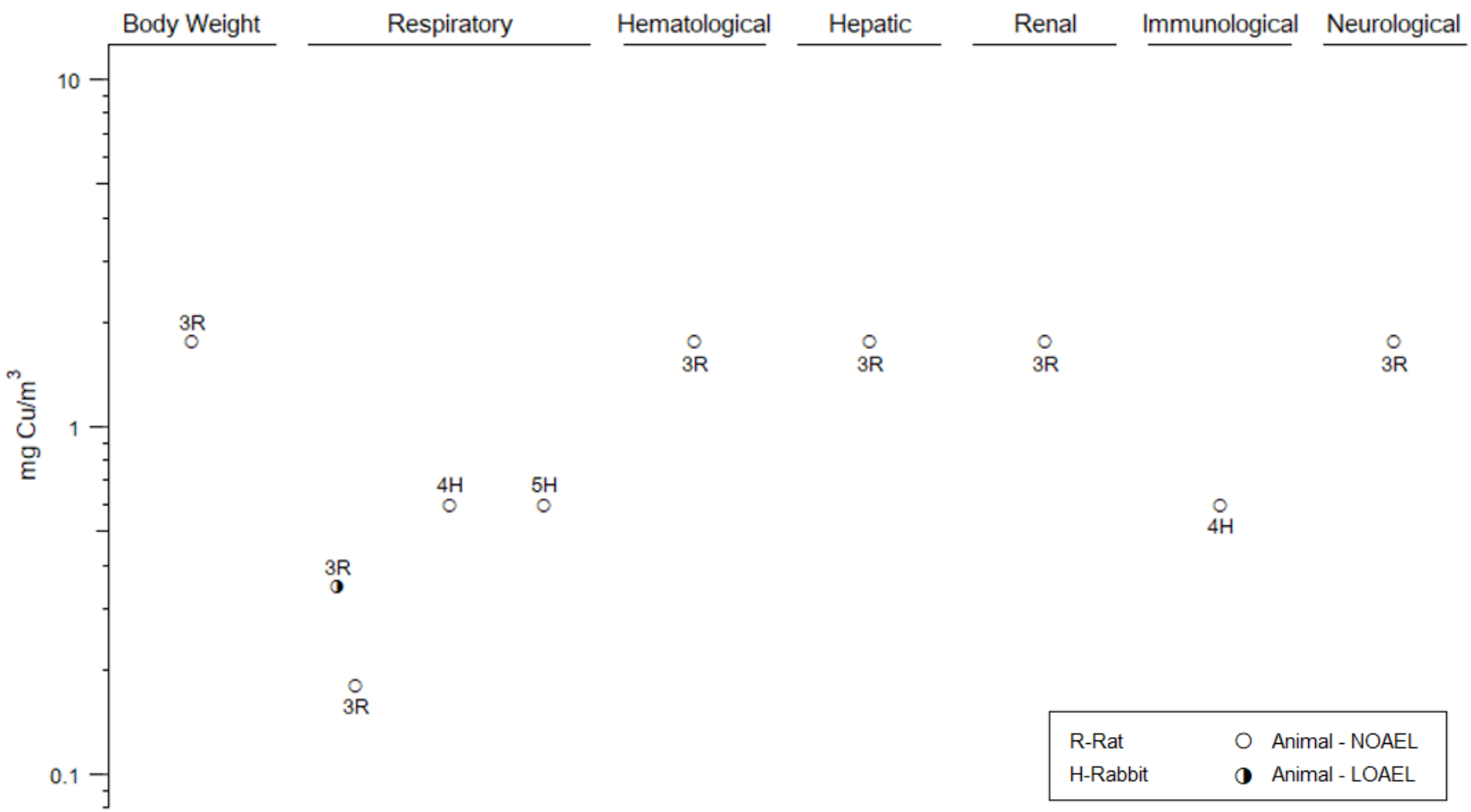


Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Araya et al. 2001									
1	Human 179 B	Once (W)	0, 0.006, 0.012, 0.018, 0.025	CS	Gastro	0.012	0.018		Significantly increased frequency of nausea, 17/179 subjects
Araya et al. 2003a									
2	Human 15 M, 15 F	Once (W)	0, 0.046	OF	Gastro		0.046		Nausea in 9/30 subjects and delayed gastric emptying
Araya et al. 2003c									
3	Human 269 F	Once (W)	0, 0.006, 0.012, 0.018, 0.025	CS, WI	Gastro	0.012	0.018		Nausea in 50/269 subjects.
Gotteland et al. 2001									
4	Human 15 M, 16 F	Once (W)	0, 0.03	CS, OF	Gastro		0.03		Nausea (6/31 subjects) and vomiting (2/31 subjects)
Olivares et al. 2001									
5	Human 30 M, 31 F	Once (W)	0, 0.006, 0.012, 0.018, 0.025, 0.031, 0.037	CS	Gastro	0.006	0.012		Nausea in 5/53 participants
Pizarro et al. 1999									
6	Human 60 F	2 weeks, daily (W)	0.0006, 0.03, 0.07, 0.1	CS, BW, BI	Bd wt	0.1			
					Gastro	0.03	0.07[b]		Abdominal pain, nausea, and/or vomiting
					Hemato	0.1			
					Hepatic	0.1			
Pizarro et al. 2001									
7	Human 45 F	1 week, daily (W)	0, 0.1	CS, BI	Gastro		0.1		Nausea, vomiting, and/or abdominal pain
					Hepatic	0.1			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Abdel-Baky 2019									
8	Rat (Wistar Albino) 6 M	2 weeks (G)	0, 25.5, 50.9	BC	Renal		25.5		Increased serum urea, uric acid, and creatinine
					Repro		25.5		Decreased serum total testosterone, FSH, LH, and prolactin
Alharbi et al. 2019									
9	Rat (albino) 10 F	7 days, daily (NS)	0, 119	BC, BI, HP	Renal			119	Severely damaged glomeruli corpuscles, hyperplasia of the epithelial cells lining the partial layer of Bowman's capsule, and severely damaged epithelial lining of the proximal and distal convoluted tubules; increased serum urea, creatinine and uric acid levels
Alhusaini et al. 2018a									
10	Rat (Albino) 6 M	7 days, daily (NS)	0, 119	BC, BI, HP	Hepatic		119		Increased hepatic ALT activity
Alhusaini et al. 2018b									
11	Rat (Albino) 8 M	7 days, daily (NS)	0, 39.8	BI, OW, HP	Hepatic			39.8	Marked cellular degeneration and hepatocyte necrosis; increased serum AST, ALT, and LDH activities
Haywood 1980									
12	Rat (NS) 2–4 M	1–2 weeks (F)	0, 300	GN, HP	Hepatic		300		Parenchymal cell hypertrophy
					Renal	300			
Haywood and Comerford 1980									
13	Rat (NS) 4 M	1–2 weeks (F)	0, 300	BC	Hepatic		300		Increased serum ALT activity

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Husain et al. 2021									
14	Rat (Wistar) 6 M	Once (W)	0, 2.4, 7.1, 14, 19	LE, HP	Gastro	7.1	14		Histopathological changes in the duodenum (loss of regular arrangement of enterocytes and their brush borders, necrotic debris, and increased lymphocytes and plasma cells)
Husain et al. 2023									
15	Rat (Wistar) 6 M	Once (GW)	0, 2, 7.1, 14, 19	LE, BC, HP	Renal		2		Mild interstitial bleeding in kidneys; increased BUN and serum creatinine
Sarawi et al. 2022									
16	Rat (Wistar) 8 M	7 days (G)	0, 39.8	BC, BI, HP, RX	Repro			39.8	Absence of mature spermatozoa, degeneration of seminiferous tubules, and loss of spermatogenic series; decreased serum FSH, LH, and testosterone
Al-Musawi et al. 2022									
17	Mouse (BALB/c) 6 M	2 weeks (G)	0, 6.4, 8.9	BW, OW, HP, RX	Bd wt			6.4	28% decrease in body weight
					Repro			6.4	Infertility
Babaei et al. 2012									
18	Mouse (NMRI) 6 F	14 days, daily (G)	0, 39.8, 79.6	BC, HP	Repro			39.8	Decreased number of antral follicles and ovarian cell damage
Kadammattil et al. 2018									
19	Mouse (Swiss albino) F NS	7 days, daily (days 7–12 of pregnancy) (NS)	0, 4.0	DX, RX	Repro	4			
					Develop	4			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kadammattil et al. 2018									
20	Mouse (Swiss albino) 2 NS	Once (NS)	39.8	LE	Death			39.8	LD_{50} (up and down method)
Kadammattil et al. 2018									
21	Mouse (Swiss albino) M NS	Once	0, 4.0	RX	Repro	4			
Yamamoto et al. 2004									
22	Shrew (*Suncus murinus*) 4 F	Once (G)	0, 2.5, 31	CS, FI	Gastro	2.5	31		15 episodes of emesis in 4/4 animals
INTERMEDIATE EXPOSURE									
Araya et al. 2003b, 2004									
23	Human 327–355 B	2 months, daily (W)	0, 0.001, 0.055, 0.11, 0.17	CS, WI, BC, BI	Gastro	0.055	0.11		Significant increase in gastrointestinal symptoms (65/355 subjects)
					Hepatic	0.17			
Harvey et al. 2003									
24	Human 12 M	6 weeks, daily (F)	0.009 (control), 0.02, and 0.08	HE, BC, BI	Hemato	0.02			
O'Connor et al. 2003									
25	Human 11 M, 11 F	6 weeks, daily (F)	M: 0.018, 0.058; F: 0.017, 0.067	BW, BC, BI	Hepatic	0.067 F 0.058 M			
Olivares et al. 1998									
26	Human 48–80 B	9 months, daily (W)	0.0378–0.174, 0.0522–0.319	CS, BW, BC	Bd wt	0.319			
					Gastro	0.319			
					Hepatic	0.319			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Pratt et al. 1985									
27	Human 3 M, 4 F	12 weeks (C)	0, 0.15	BC	Gastro	0.15			
					Hemato	0.15			
					Hepatic	0.15			
Rojas-Sobarzo et al. 2013									
28	Human 30 M	6 months	0, 0.1	BC, BI	Hepatic	0.1			
Abe et al. 2008									
29	Rat (Fischer-344) 6–8 M	6 weeks daily (F)	0, 62	BW, HP	Bd wt	62			
					Hepatic	62			
Adele et al. 2023									
30	Rat (Wistar) 5 F	5 weeks (NS)	0, 39.8	BW, HE, OW	Bd wt	39.8			
					Hemato		39.8		Decreased erythrocyte count, hemoglobin, and hematocrit
					Hepatic	39.8			
					Immuno		39.8		Decreased WBC count
Ali et al. 2023									
31	Rat (Sprague-Dawley) 4 F	4 months (W)	0, 11.3	HP	Cardio			11.3	Increased cardiac injury score (myocyte damage and necrosis), mast cell infiltration and collagen deposition in the heart
Ali et al. 2023									
32	Rat (Sprague-Dawley) 6 F	4 months (W)	0, 11.3	BW, OW, HP	Bd wt	11.3			
					Cardio			11.3	Fibrosis and collagen deposition in the heart; myocardial damage; increased absolute and relative heart weight

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Arafa et al. 2019									
33	Rat (Wistar) 10 M	90 days, daily (G)	0, 50.9	CS, BI, HP	Cardio		50.9		Increase in systolic blood pressure
					Repro			50.9	Reductions in relative testicular weight, serum testosterone, and serum LH
Arowoogun et al. 2021									
34	Rat (Wistar) 5 M	7 weeks 3 times/week (GO)	0, 79.6	BW, HP	Neuro			79.6	Focal areas of necrosis and degenerated neurons in the cerebellum (not reported quantitatively); ~35% decrease in brain AChE activity
Babaei and Abshenas 2013									
35	Rat (Sprague-Dawley) 12 M	56 days, daily (G)	0, 79.6	OW, HP, RX	Repro			79.6	Reduced testicular weight; decreased sperm count, percentage of live spermatozoa, and sperm motility
Chen et al. 2023									
36	Rat (Wistar) 10 F	35 days (G)	0, 6, 12, 25	OW, HP	Bd wt	6	12		10% decrease in body weight
					Repro		6		Decreased percentage preantral ovarian follicles; increased percentages of antral and atretic follicles
Chung et al. 2009									
37	Rat (Sprague-Dawley) 12 M, 12 F	M: 30 days F: 38 days (GW)	0, 0.83, 3, 13, 51	LE, CS, BW, FI, HE, BC, UR, GN, OW, HP, RX, DX	Death			51 F	3/12 died
					Bd wt	51			
					Resp	51			
					Cardio	51			
					Gastro	0.83 F	3 F		Increased incidences of squamous cell hyperplasia in the stomach
						3 M	13 M		Increased incidences of squamous cell hyperplasia in the stomach

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	51 F			
						13 M	51 M		Decreased erythrocyte count, hemoglobin, hematocrit, MCV, and MCH; increased platelets, WBCs, and neutrophils
					Hepatic	51			
					Renal	51			
					Endocr	51			
					Immuno	51			
					Neuro	51			
					Repro	51			
					Develop	13	51		Increased percentage of runt pups (weighing 1/3 less than control mean weight) and pups with icterus
De Vries et al. 1986									
38	Rat (Sprague-Dawley) 8 F	11 months, daily (W)	0, 46	BI	Neuro		46		Decreased 3,4-dihydroxyphenylacetic acid levels in corpus striatum
Draper et al. 2023									
39	Rat (Sprague-Dawley) 6 M	28 days (GW)	0, 161.5	HP	Resp		161.5		Slight histological changes in the lungs (thickened interalveolar septa, stratified epithelia, smooth muscle disruption, epithelial desquamation)
Epstein et al. 1982									
40	Rat (Sprague-Dawley) 8 M	90 days, daily (W)	0, 8.6	BW, WI, BC	Bd wt	8.6			
					Hepatic		8.6		Increased serum AST activity

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Fuentealba et al. 2000									
41	Rat (Fischer-344) 4–5 M, 4–11 F	12–18 weeks (F)	Young rats, M: 0, 150; F: 0, 170 Adult rats, M: 0, 120; F: 0, 130	BC, HP, DX	Death			150 F	2/8 young female rats died during experiment
					Hepatic			120 M	Multifocal hepatitis, widespread single cell necrosis, and increased serum ALT and SDH activities in adult rats after 18 weeks
Gupta et al. 2021									
42	Rat (Wistar) 5 M	24 weeks (GW)	0, 8.0	BW, FI, WI, BC, BI, OW, HP, RX	Bd wt	8			
					Repro			8	Shrunken seminiferous tubules; decreases in the following: absolute testis weight, sperm count, percent motile sperm, and percent viable sperm; and an increase in morphological abnormalities in sperm
Haywood 1980									
43	Rat (NS) 2–4 M	3–15 weeks (F)	0, 180	GN, HP	Hepatic			180	Massive necrosis, inflammatory cell infiltration, bile duct hyperplasia, progressing to fine diffuse fibrosis by 15 weeks
					Renal		180		Cytoplasmic droplets and desquamation of epithelial cells in proximal tubules
Haywood and Comerford 1980									
44	Rat (NS) 4 M	3–15 weeks (F)	0, 180	BC	Hepatic		180		Increased ALT activity
Haywood and Loughran 1985									
45	Rat (Wistar) 24 M	5–15 weeks (F)	0, 320, 420, 530, 640	BW, HP	Bd wt			320	~50% decrease in terminal body weight
					Hepatic			320	Diffuse and extensive necrosis by week 5

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kalita et al. 2020									
46	Rat (Wistar) 6 M	1 month, daily (G)	0, 25.5	BW, BI, HP, NX	Bd wt	25.5			
					Neuro			25.5	Reduced locomotor activity (reduced distance traveled and time moving); reduced grip strength; and reduced latency to fall time on the rotarod test and increased time resting
Kumar and Sharma 1987									
47	Rat (Albino) 15 M	30 days, daily (G)	0, 39.8	BW, BC, BI	Hemato		39.8		Decreased erythrocyte count and hemoglobin
					Hepatic		39.8		Increased serum ALT with increased cholesterol and bilirubin and decreased total protein levels
					Renal		39.8		Increased urea levels
Kumar et al. 2015, 2016a, 2016b									
48	Rat (Wistar) 18 M	30, 60, or 90 days, daily (G)	0, 25.5, 50.9	BW, BC, HE, HP, NX	Bd wt			25.5	26% decrease in body weight at 90 days
					Hemato		25.5		Decreased hemoglobin at 60 and 90 days
					Hepatic			25.5	Hepatocellular degeneration and hemorrhage, massive fatty change and centrilobular necrosis, occasional hepatic cell necrosis; increased ALT, AST, and bilirubin at 90 days
					Renal			25.5	Hemorrhage, inflammatory and cellular damage in kidneys, and degeneration of renal intertubular space and Bowmen's capsule; increased BUN and BUN/creatinine ratio after 90 days

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Neuro			25.5	Impaired motor coordination and cognitive function (grip strength, latency to fall time, and attention scores); gliosis; pyknotic nuclei, and glial nodule formation in brain after 90 days
Kumar et al. 2019									
49	Rat (Sprague-Dawley) 5 M	16 weeks, daily (G)	0, 2.6, 5.1	CS, BW, BC, NX	Bd wt	5.1			
					Neuro			2.6	Decreased locomotor activity and neuromuscular coordination, decreased passive avoidance response, less exploration time
Liu and Medeiros 1986									
50	Rat (Wistar) 10 M	15 weeks (F)	0, 14	CS, BW, FI, WI, BC, UR, OW	Cardio		14		Increased blood pressure
Liu et al. 2016									
51	Rat (Wistar) 10 M	30 days, daily (G)	0, 39.8, 79.6, 159	OW, HP, RX	Repro		39.8	79.6	LOAEL: Decreased sperm count and serum LH and FSH SLOAEL: Marked reduction in sperm count and increase in sperm malformation rate; significant reductions in serum testosterone, FSH, and LH
Llewellyn et al. 1985									
52	Rat (Holtzman) 10 M	21 weeks (F)	0, 120	BW, FI, WI, OW	Bd wt		120		Decreased body weight gain (23%)
					Musc/skel	120			
Murthy et al. 1981									
53	Rat (NS) 48 M	Daily, 30 days (F)	0, 23	CS, BW	Neuro		23		Increase in dopamine and norepinephrine with 21% casein diet, and decrease in 5-hydroxy-tryptamine with 10% casein diet

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1993									
54	Rat (Fischer-344) 5 M, 5 F	6–15 days, daily (W)	M: 0, 10, 29, 36, 45, 96; F: 0, 10, 26, 31, 71	CS, BW, WI, GN, HP	Death			31 F	5/5 died
								36 M	5/5 died
					Bd wt	26 F		31 F	46% decrease in body weight
						29 M		36 M	48% decrease in body weight
					Resp	26 F			
						29 M			
					Cardio	26 F			
						29 M			
					Gastro	26 F			
						29 M			
					Hepatic	26 F			
						29 M			
					Renal	26 F			
							10 M		Protein droplets in epithelial cells of proximal tubule
					Endocr	26 F			
						29 M			
					Immuno	26 F			
						29 M			
					Neuro	26 F			
						29 M			
					Repro	26 F			
						29 M			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1993									
55	Rat (Fischer-344) 5 M, 5 F	15 days, daily (F)	M: 0, 23, 46, 92, 198, 324; F: 0, 23, 44, 93, 196, 285	CS, BW, FI, WI, GN, OW, HP	Bd wt	196 F	285 F		13% decrease in body weight
						92 M	198 M		18% decrease in body weight
					Resp	285 F			
						324 M			
					Cardio	285 F			
						324 M			
					Gastro	23 F	44 F		Hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach
						23 M	46 M		Hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach
					Hemato	93 F		196 F	Depletion of hematopoietic cells in bone marrow
						92 M		198 M	Depletion of hematopoietic cells in bone marrow
					Hepatic	196 F	285 F		Minimal to mild mononuclear inflammatory cell infiltrate in three of five females
						92 M	198 M		Minimal to mild mononuclear inflammatory cell infiltrate in 4/5 males
					Renal	44 F	93 F		Increased protein droplets in cortical tubules
						46 M	92 M		Increased protein droplets in cortical tubules

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	285 F			
						324 M			
					Immuno	285 F			
						324 M			
					Neuro	285 F			
						324 M			
					Repro	285 F			
						324 M			
NTP 1993									
56	Rat (Fischer-344) 10 M, 10 F	13 weeks, daily (F)	M: 0, 8, 16, 33, 66, 140 F: 0, 9, 17, 34, 68, 134	CS, BC, BI, UR, GN, OW, HP	Bd wt	134 F			
						66 M		140 M	24% decrease in body weight by end of experiment
					Resp	134 F			
						140 M			
					Cardio	134 F			
						140 M			
					Gastro	17 F	34 F		In 7/10 females, hyperplasia of limiting ridge that forms the junction of the forestomach squamous mucosa with the glandular gastric mucosa
						16 M	33 M		In 10/10 males, hyperplasia of limiting ridge that forms the junction of the forestomach squamous mucosa with the glandular gastric mucosa
					Hemato	134 F			
						33 M	66 M		Decreased hematocrit, hemoglobin, mean cell volume and mean cell hemoglobin levels; and increased reticulocytes and platelets

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	34 F		68 F	Chronic active inflammation with focal necrosis in 1/10 males; increased serum ALT
						16 M	33 M		Chronic active inflammation with focal necrosis in 1/10 males; 112% increase in serum ALT
					Renal	9 F	17 F		Increased BUN and cytoplasmic alteration in kidneys of 1/10 females
						16 M	33 M		Cytoplasmic alteration in kidneys of 3/10 males
					Endocr	134 F			
						140 M			
					Neuro	68 F		134 F	Gliosis in brain in 10/10 rats
						140 M			
					Repro	68 F 140 M		134 F	Chronic active inflammation of clitoral gland in 10/10 rats
Parlak Ak et al. 2021									
57	Rat (Sprague-Dawley) 6 M	21 days (G)	0, 127	OW, HP, RX	Repro			127	Histopathological changes in the testes (shrinkage of seminiferous tubules, vacuoles, loss of germ cells, interstitial edema); decreased sperm concentration and motility; and increased percentage of abnormal sperm
Patwa and Flora 2020									
58	Rat (Sprague-Dawley) 9 M	16 weeks (GW)	0, 8.0	BW, BC, BI, OW, HP, IX	Bd wt	8			
					Hepatic			8	Marked necrosis of hepatocytes, distorted sinusoidal space, and central vein distortion in liver

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Patwa et al. 2022									
59	Rat (Sprague-Dawley) 6 M	16 weeks (NS)	0, 8	NX	Neuro			8	Decreased spontaneous locomotor activity in open field test, impaired memory function in passive avoidance and novel object exploration tests, increased anxiety in elevated plus maze test
Rana and Kumar 1980									
60	Rat (Albino) 10 M	20 days, daily (G)	0, 39.8	CS, BW, BC, GN, HP	Bd wt			39.8	>28% decrease in body weight
					Hemato		39.8		Decreased erythrocyte count, hemoglobin, and hematocrit
					Musc/skel		39.8		Depressed skeletal growth assessed by tail length
					Hepatic			39.8	Centrilobular necrosis and perilobular sclerosis with nuclear edema in liver
					Renal		39.8		Engorgement of uriniferous tubules, necrosis of the tubules, nuclear pyknosis and cell proliferation in medullary region
Sakhaee et al. 2012									
61	Rat (Wistar) 20 M	8 weeks, daily (G)	0, 39.8, 79.6	BC, BI, HP, RX	Hepatic			39.8	Multifocal hepatitis, cell swelling in hepatocytes, centrilobular hepatocellular necrosis, and mild bile retention
					Renal		39.8		Mild tubular necrosis and hyaline cast formation in renal tubules
					Repro			39.8	Decreases in sperm concentration, motility, and viability
Seven et al. 2018									
62	Rat (Sprague-Dawley) 6 M	21 days, daily (G)	0, 199	BW, BI, HP	Bd wt	199			
					Other noncancer		199		Decreased food consumption

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Seven et al. 2020									
63	Rat (Sprague-Dawley) 6 M	21 days (GW)	0, 128	OW, HP, NX	Repro			128	Histopathological changes in the testes (loss, disorganization and vacuolation of germinal epithelium; interstitial edema); decreased sperm concentration and percent motile sperm; increased percentage of abnormal sperm
Sugawara et al. 1995									
64	Rat (Fischer-344) 6 F	60 days (F)	0.124, 17, 34, 68	BW, BC	Hepatic	17	34		Increased serum ALT and AST activities
Temiz et al. 2021									
65	Rat (Wistar Albino) 8 M	2 times/week 28 days (G)	0, 3.9	BC, BI, HP	Hepatic		3.9		Increased serum AST, ALT, and LDH; centrilobular and vacuolar degeneration, dilatation of sinusoid, focal necrosis, and inflammatory cell infiltration in all or most animals
Yu et al. 2021a									
66	Rat (Sprague-Dawley) 24 M	24 weeks (F)	15, 30, 60, 120	BW, BC, BI, OW, HP	Hepatic	30	60		Decreased hepatocyte count and percentage of hepatocyte area; hepatic cords were damaged, disordered or even absent, and increased number of cells with hyperchromatic nuclei and concentrated cytoplasm

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Yu et al. 2023									
67	Rat (Sprague-Dawley) 10 M	12 weeks (G)	0, 20, 40, 80, 160	BW, FI, HP, NX	Bd wt		160		11% decrease in terminal body weight
					Neuro	40		80	Impaired spatial learning and memory (assessed in Morris water maze test); histopathological changes in the brain (pyknosis, hyperemia, neuronal edema, vacuolation)
Adeleke et al. 2023									
68	Mouse (Swiss) 10 M	28 days (G)	0, 10, 20, 39.8	HP, NX	Neuro			10	Decreased density of viable neurons in the brain; increased immobility in the tail suspension and forced swim tests
Babaei et al. 2012									
69	Mouse (NMRI) 6 F	35 days, daily (G)	0, 39.8, 79.6	BC, HP	Repro			39.8	Significant decrease in number of ovarian follicles and corpus lutea, and ovarian cell damage
Chen et al. 2020									
70	Mouse (CD-1) 15 M	8 weeks (G)	0, 10, 39.8, 59.7	BC, HP, RX	Repro	10	39.8		Decreased sperm count and sperm motility
Dab et al. 2023									
71	Mouse (Swiss (albino)) 8 M	20 days (G)	0, 16	BW, BC	Bd wt		16		Decreased body weight gain (78%)
					Hepatic		16		Increased serum ALT
Dai et al. 2020									
72	Mouse (C57BL/6) 10 M	28 days (G)	0, 12.8, 25.5, 50.9	BW, BC, BI, OW, HP	Bd wt	50.9			
					Renal	12.9	25.5		Increased serum BUN and creatinine; tubular degeneration, necrosis, tubular dilation, cast formation, and glomerular degeneration

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dai et al. 2023									
73	Mouse (C57BL/6) 10 M	28 days (NS)	0, 39.8	LE, BW, OW, HP	Bd wt		39.8		~10% decrease in body weight
					Renal			39.8	Severe tubular dilation, degeneration, and necrosis; increased BUN and serum creatinine
Guo and Wang 2021									
74	Mouse (ICR) 60 M	42 days (G)	0, 3.9, 7.8, 15.6	OW, HP, RX	Repro		3.9		Increased sperm malformations and decreased sperm motility and concentration
Isibor et al. 2022									
75	Mouse (Swiss) 10 M	28 days (GW)	0, 39.8	BI, NX	Neuro		39.8		Impaired spatial memory function (Y-maze test); 60% increase in brain AChE activity
Kheirandish et al. 2014									
76	Mouse (NMRI) 15 M	56 days, daily (G)	0, 79.6	GN, HP	Repro			79.6	Shrinkage of seminiferous tubules and moderate to severe degeneration of germinal layers, significantly decreased seminiferous tubule diameter, Sertoli cell nuclei diameter and epithelial height; and significantly lower meiotic index and spermatogenesis
Kvietkauskaite et al. 2004									
77	Mouse (BALB/c) 10 M	19 weeks (W)	0, 22, 42	BW, HE, BC, BI, OW, HP	Bd wt	22	42		10.3% decrease in body weight
					Hemato	42			
					Immuno		22		Decreased percent of natural killer and suppressor cells and altered immunoregulatory index

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Liu et al. 2020a, 2020b, 2021a, 2021b									
78	Mouse (ICR) 4 M, 4 F	21 or 42 days (GW)	0, 4, 8 or 16	BW, BC, OW, HP	Bd wt		4	8	LOAEL: 15% decrease in terminal body weight SLOAEL: >20% decrease in terminal body weight
					Hepatic	4	8		Disorganized hepatic cords, hepatocyte degeneration (granular and vacuolar)
NTP 1993									
79	Mouse (B6C3F1) 5 M, 5 F	8–15 days, daily (W)	M: 0, 10, 24, 57, 133, 367; F: 0, 15, 36, 62, 174, 330	BW, WI, GN, HP	Death			62 F	3/5 died
								57 M	1/5 died
					Bd wt	36 F		62 F	34% weight loss in survivors
						24 M		57 M	22% weight loss
					Resp	36 F			
						24 M			
					Cardio	36 F			
						24 M			
					Gastro	36 F			
						24 M			
					Hepatic	36 F			
						24 M			
					Renal	36 F			
						24 M			
					Endocr	36 F			
						24 M			
					Neuro	36 F			
						24 M			
					Repro	36 F			
						24 M			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 1993									
80	Mouse (B6C3F1) 5 M, 5 F	15 days, daily (F)	M: 0, 43, 92, 197, 294, 717; F: 0, 53, 104, 216, 398, 780	CS, BW, FI, WI, GN, OW, HP	Bd wt	780 F			
						717 M			
					Resp	780 F			
						717 M			
					Cardio	780 F			
						717 M			
					Gastro	104 F	216 F		Two of five females had minimal hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge of the forestomach at its junction with the glandular gastric mucosa
						92 M	197 M		Three of five males had minimal hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge of the forestomach at its junction with the glandular gastric mucosa
					Renal	780 F			
						717 M			
NTP 1993									
81	Mouse (B6C3F1) 10 M, 10 F	13 weeks, daily (F)	M: 0, 44, 97, 187, 398, 815; F: 0, 52, 126, 267, 536, 1,058	CS, BW, FI, GN, OW, HP	Bd wt	267 F	536 F	1,058 F	LOAEL: 12% decrease in body weight SLOAEL: 24% decrease in body weight
						97 M	187 M		10% decrease in body weight
					Resp	1,058 F			
						815 M			
					Cardio	1,058 F			
						815 M			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Gastro	126 F	267 F		In 5/10 females, hyperplasia of forestomach mucosa
						97 M	187 M		In 2/10 males, hyperplasia of forestomach mucosa
					Hepatic	1,058 F			
						815 M			
					Renal	1,058 F			
						815 M			
					Endocr	1,058 F			
						815 M			
					Neuro	267 F			
						187 M			
					Repro	536 F	1058 F		Cyst in clitoral gland in 8/10
						815 M			
Peng et al. 2020									
82	Mouse (C57BL/6) 10 M	4 weeks (GW)	0, 80.0	BC, HP	Renal			80	Increased BUN and serum creatinine; marked tubular degeneration, dilation, and necrosis in kidneys
Sakhaee et al. 2014									
83	Mouse (NMRI) 12 M	42 days, daily (G)	0, 79.6	BC, BI, GN, HP	Hepatic		79.6		Increased serum AST and ALT
					Repro			79.6	Degenerative changes in seminiferous tubules; significantly decreased sperm concentration, motility, and viability
Sakhaee et al. 2016a									
84	Mouse NMRI 6 M	28 days, once every 2 days (GW)	0, 39.8	HP, RX	Repro			39.8	Depletion and vacuolation of seminiferous epithelium; significant decreases in sperm count, motility, and viability

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Sakhaee et al. 2016a									
85	Mouse NMRI 6 M	42 days, once every 2 days (GW)	0, 39.8	HP, RX	Repro			39.8	Degeneration of the seminiferous tubules; significant decreases in sperm count, motility, and viability
Sakhaee et al. 2016b									
86	Mouse (NMRI) 6 M	42 days (GW)	0, 39.8	HP, RX	Repro			39.8	Disorganization and vacuolation of seminiferous epithelium; significant decreases in sperm count, motility, and viability
Seffner et al. 1997									
87	Guinea pig (albino) 5–8 NS	6 months, daily (W)	<1.04, 18.4	DX	Develop	18.4			
Li et al. 2021									
88	Rabbit (Rex) 20 M, 20 F	5 weeks (F)	0.60, 2.72, 4.83	BW, FI, BC, OW	Bd wt	4.83			
Aulerich et al. 1982									
89	Mink (dark mink) 12 M, 12 F	153 or 367 days (F)	M: 0, 1.5, 3, 6, 12; F: 0 1.6, 3, 6, 13	DX	Repro Develop	12 13			
Kline et al. 1971									
90	Pig (Hampshire-Yorkshire) 12 NS	88 days (F)	0.1, 1.7, 2.3, 2.7	BW, FI, HE, BC	Bd wt Hemato	1.7 2.7	2.3		Decreased body weight gain (17%)
Suttle and Mills 1966									
91	Pig (NS) 6 F	46 days, daily (F)	0, 16.5	BW, BC, BI	Bd wt Hemato Hepatic		16.5 16.5 16.5		Decreased body weight gain (22%) Decreased hemoglobin Jaundice in 2/6 animals

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Suttle and Mills 1966									
92	Pig (NS) 6 F	49 days, daily (F)	0, 18.7	BW, BC, BI	Bd wt		18.7		Decreased body weight gain (27%)
					Hemato		18.7		Decreased hemoglobin at 6 weeks, and increased erythrocyte count
					Hepatic		18.7		Severe transient jaundice 5/6 animals between weeks 3 and 6; increased AST activity
Zhang et al. 2020									
93	Pig (NS) 6 M, 6 F	6 weeks (F)	0, 0.35, 1.80, 3.62	BW, FI, BC, OW, HP	Bd wt	3.62			
					Hepatic	3.62			
CHRONIC EXPOSURE									
Araya et al. 2012									
94	Monkey (Tufted Capuchin) 2 M, 2 F	3 years daily (F)	0, 5 increased to 7.5 over first 2 months	CS, BW, FI, BI, HP, OF	Bd wt	7.5			
					Hemato		7.5		Decreased hemoglobin
					Hepatic	7.5			
Araya et al. 2012									
95	Monkey (Tufted Capuchin) 2 M, 2 F	3 years daily (milk)	0, 3.5 increased to 5.5 over first 2 months	CS, BW, FI, BI, HP, OF	Bd wt	5.5			
					Hemato	5.5			
					Hepatic	5.5			

Table 2-2. Levels of Significant Exposure to Copper – Oral (mg Cu/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Massie and Aiello 1984									
96	Mouse (C57BL/6N) 8 M	850 days (W)	0, 4.2, 8.5, 42	CS, BW	Death			42	14.4% decrease in mean survival time and 12.8% decrease in maximum lifespan
					Bd wt	42			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.02 mg Cu/kg/day based on benchmark dose modeling of gastrointestinal symptoms in volunteers. The $BMDL_{10}$ of 0.055 mg Cu/kg/day was divided by an uncertainty factor of 3 for human variability to derive the MRL. This MRL was also considered protective for intermediate-duration exposure and adopted for the intermediate-duration oral MRL. See Appendix A for more detailed information regarding the MRL.

AChE = acetyl cholinesterase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both males and females; BC = serum (blood) changes; Bd wt or BW = body weight; BI =biochemical indices; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; FSH = follicle-stimulating hormone; (G) = gavage; Gastro = gastrointestinal; GN = gross necropsy; (GO) = gavage in oil; (GW) = gavage in water; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; IX = immune function; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; LE = lethality; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SDH = sorbitol dehydrogenase; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (W) = water; WBC = white blood cell; WI = water intake

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

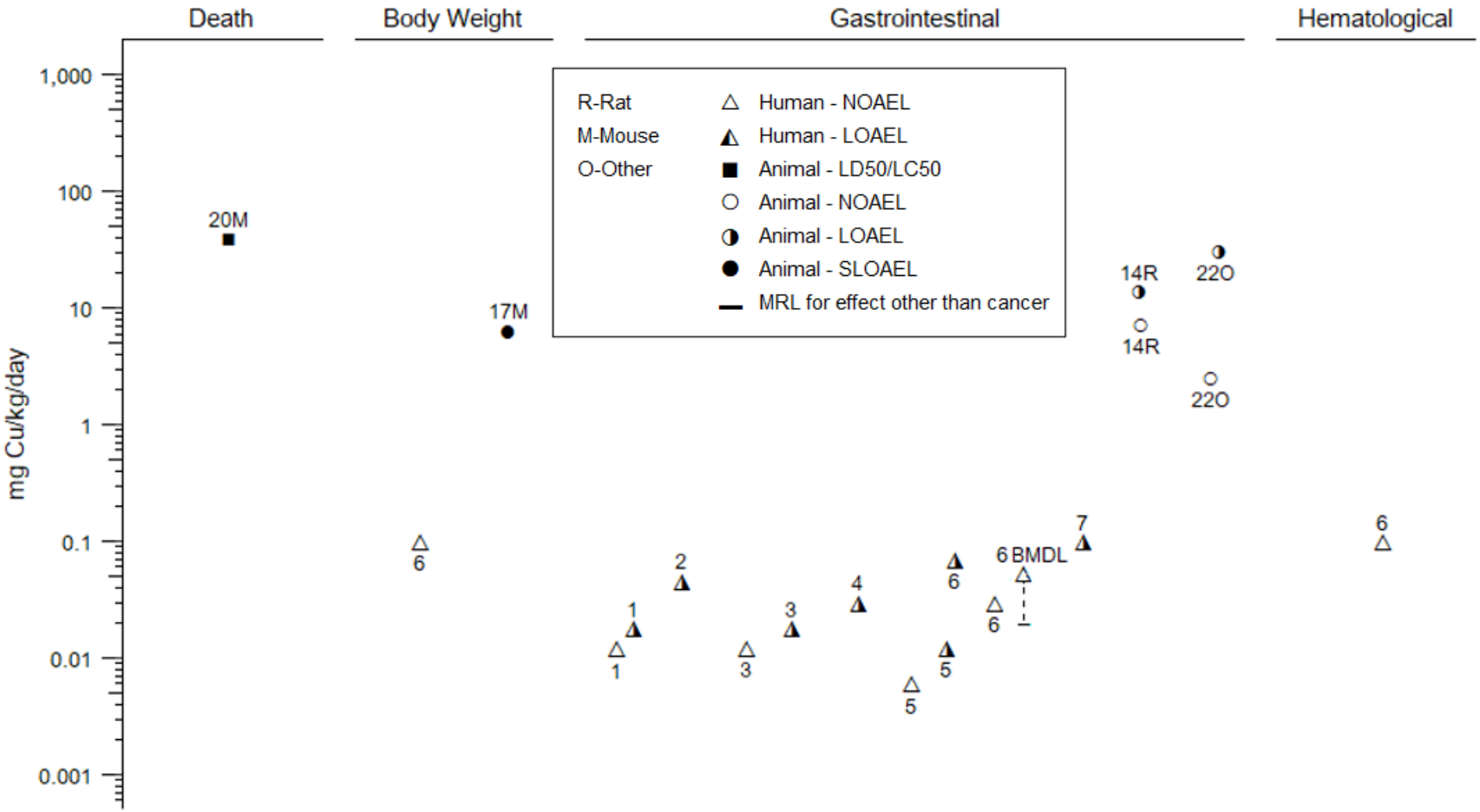


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Acute (≤14 days)

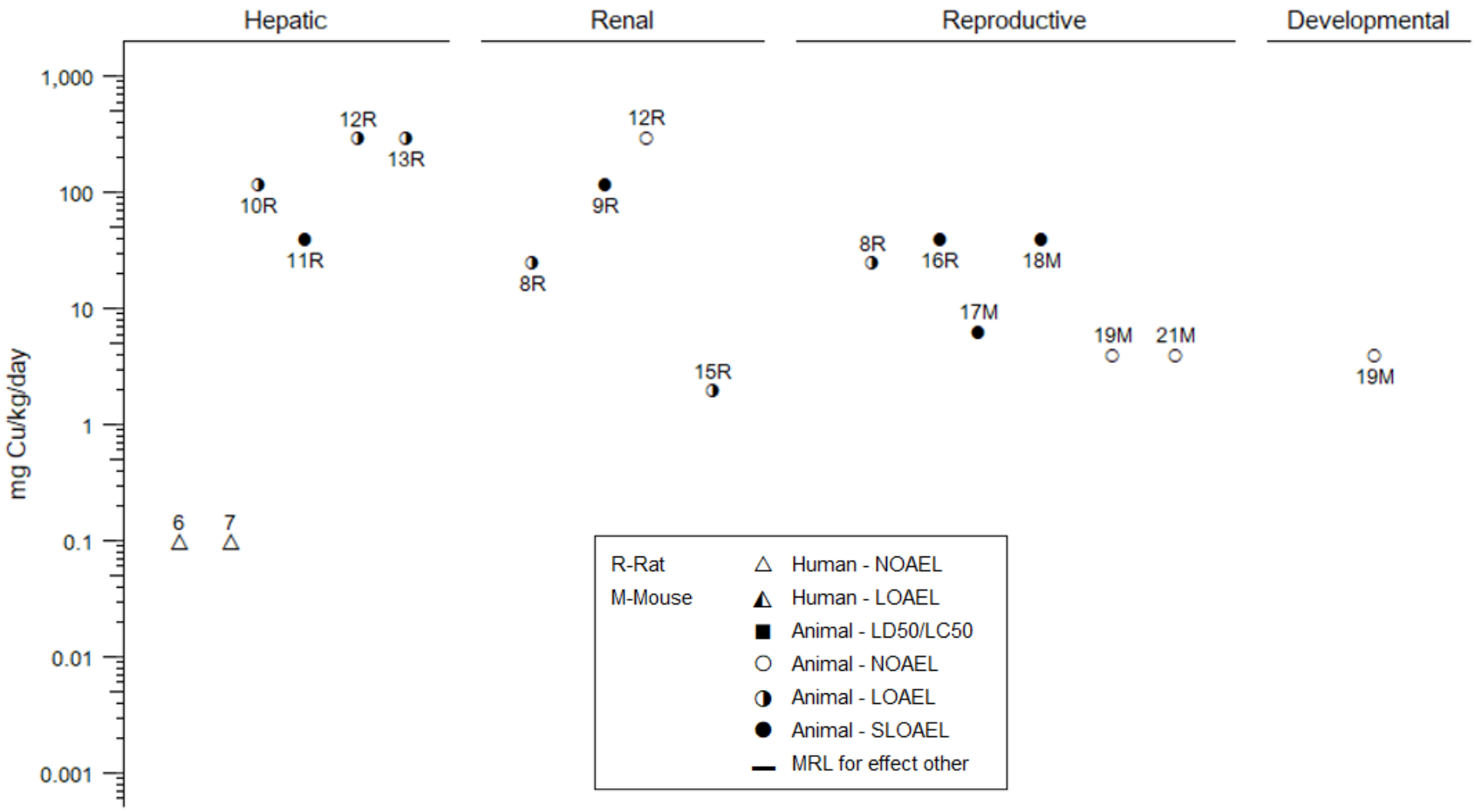


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

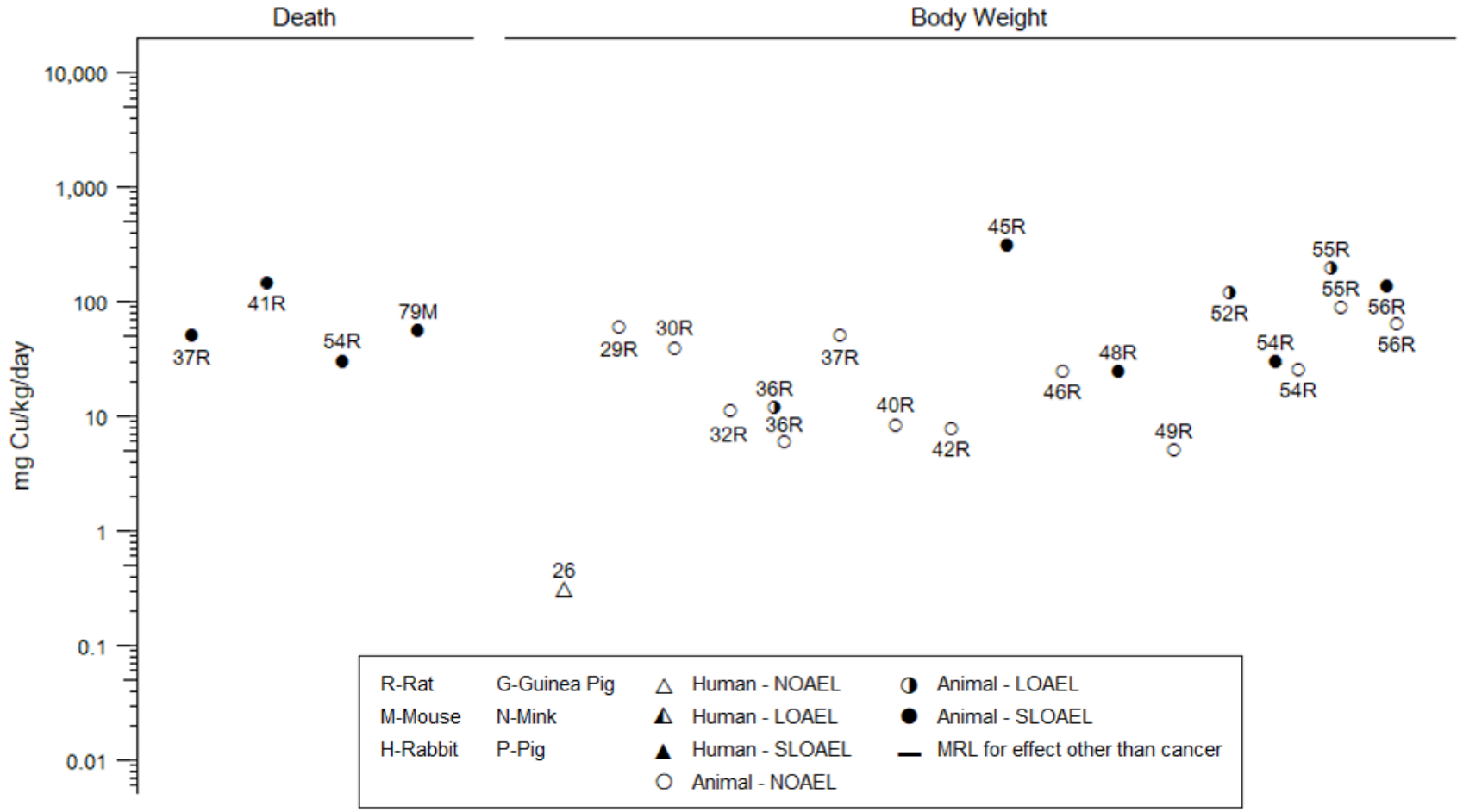


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

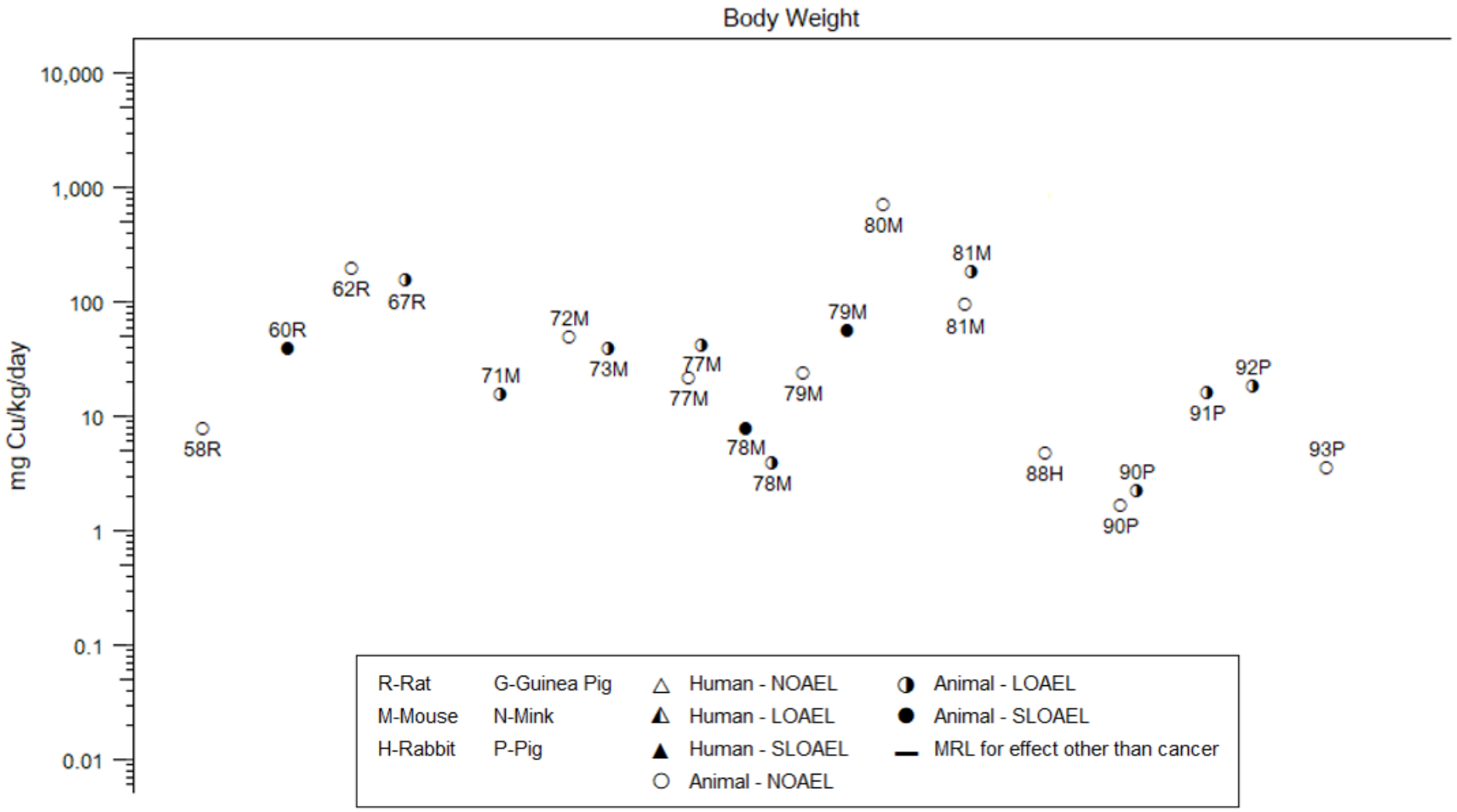


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

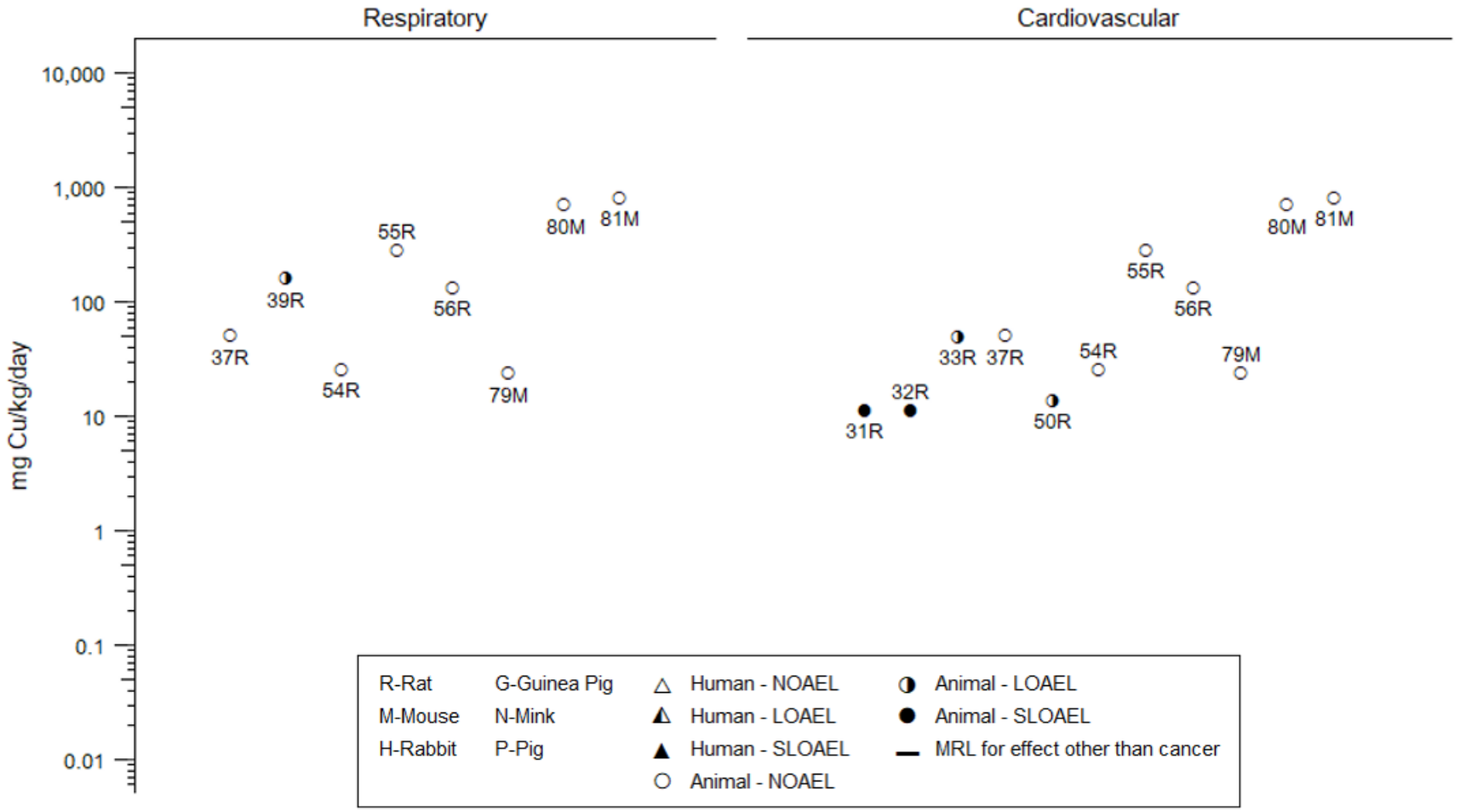


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

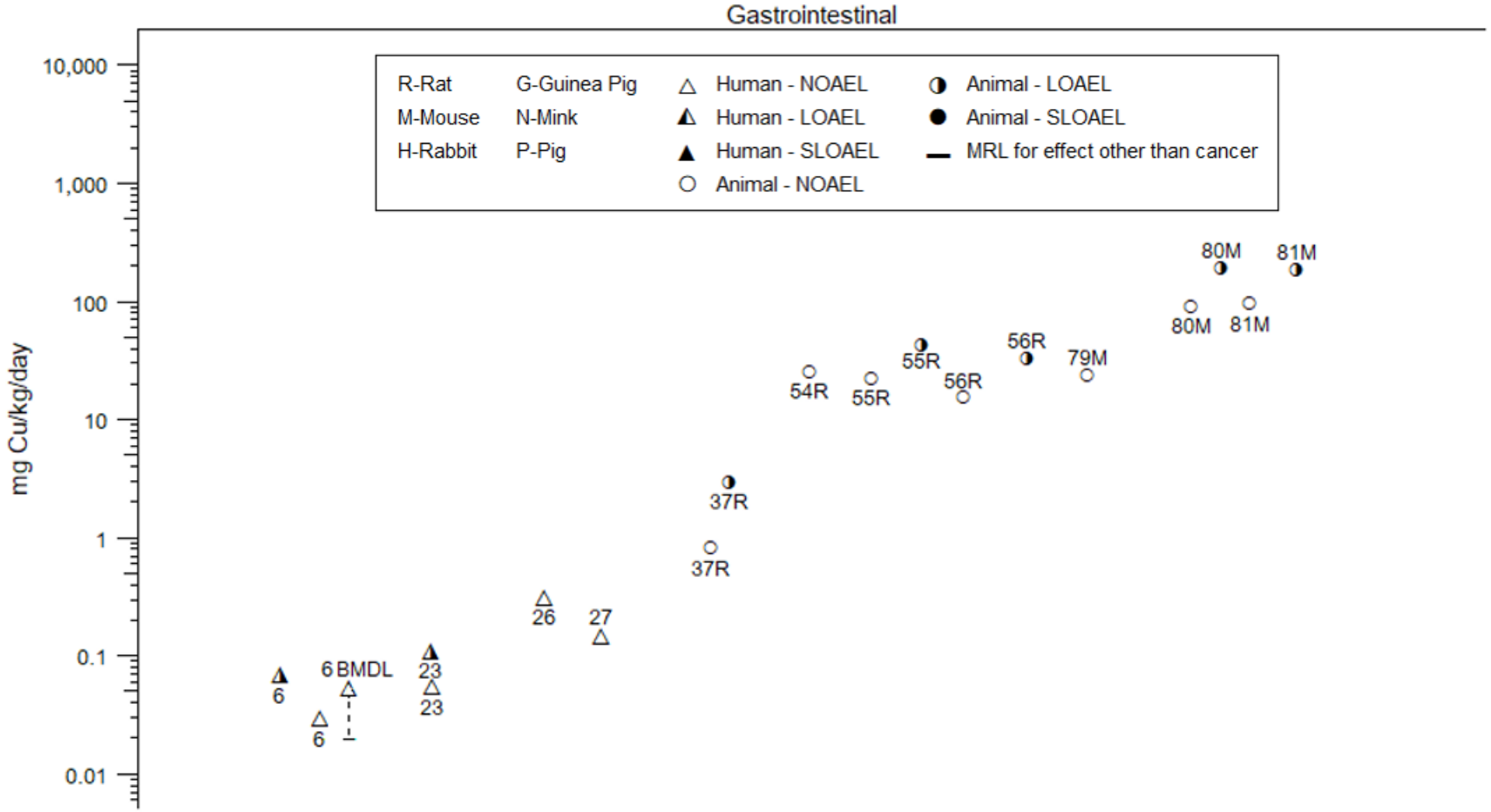


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

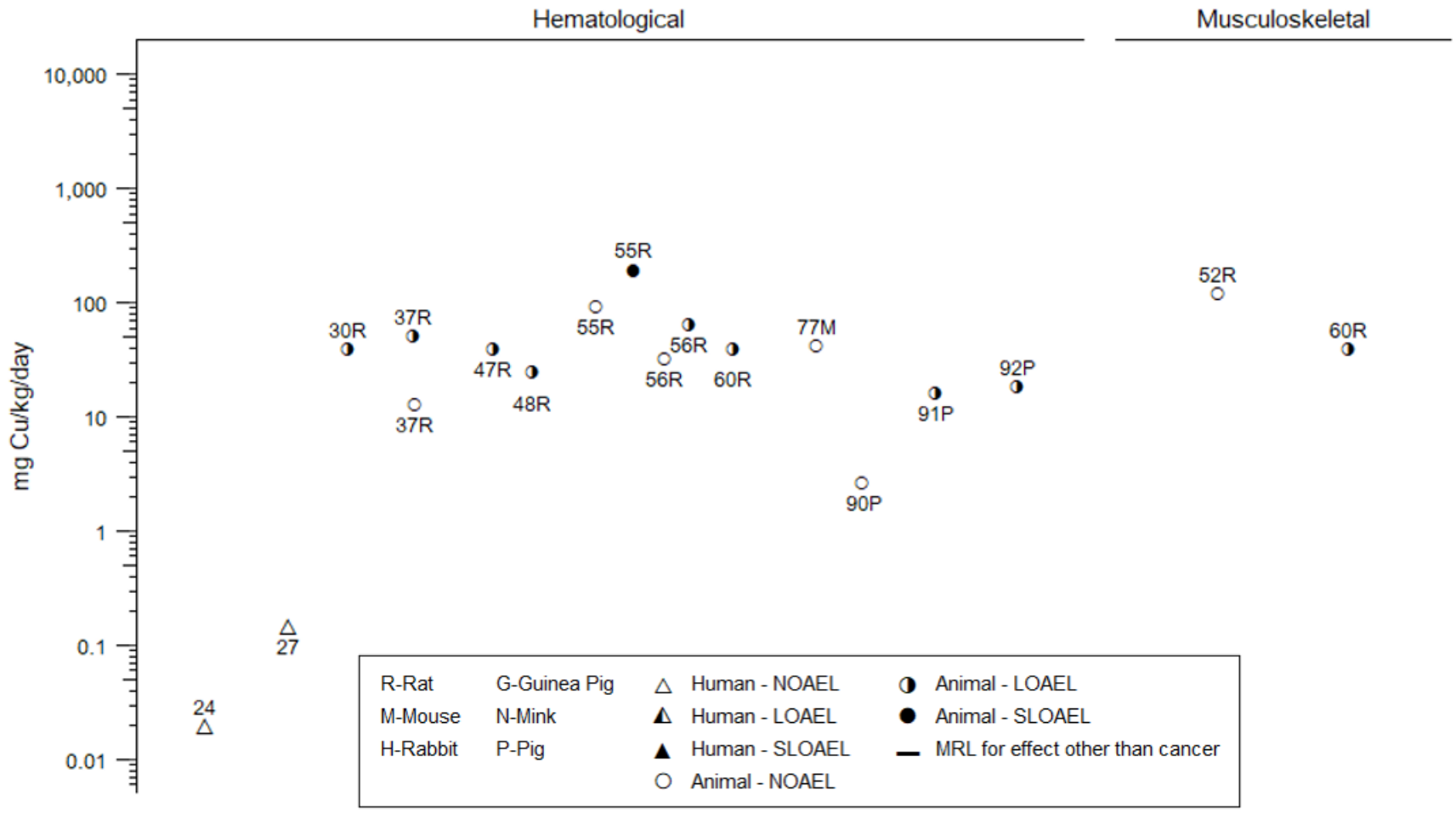


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

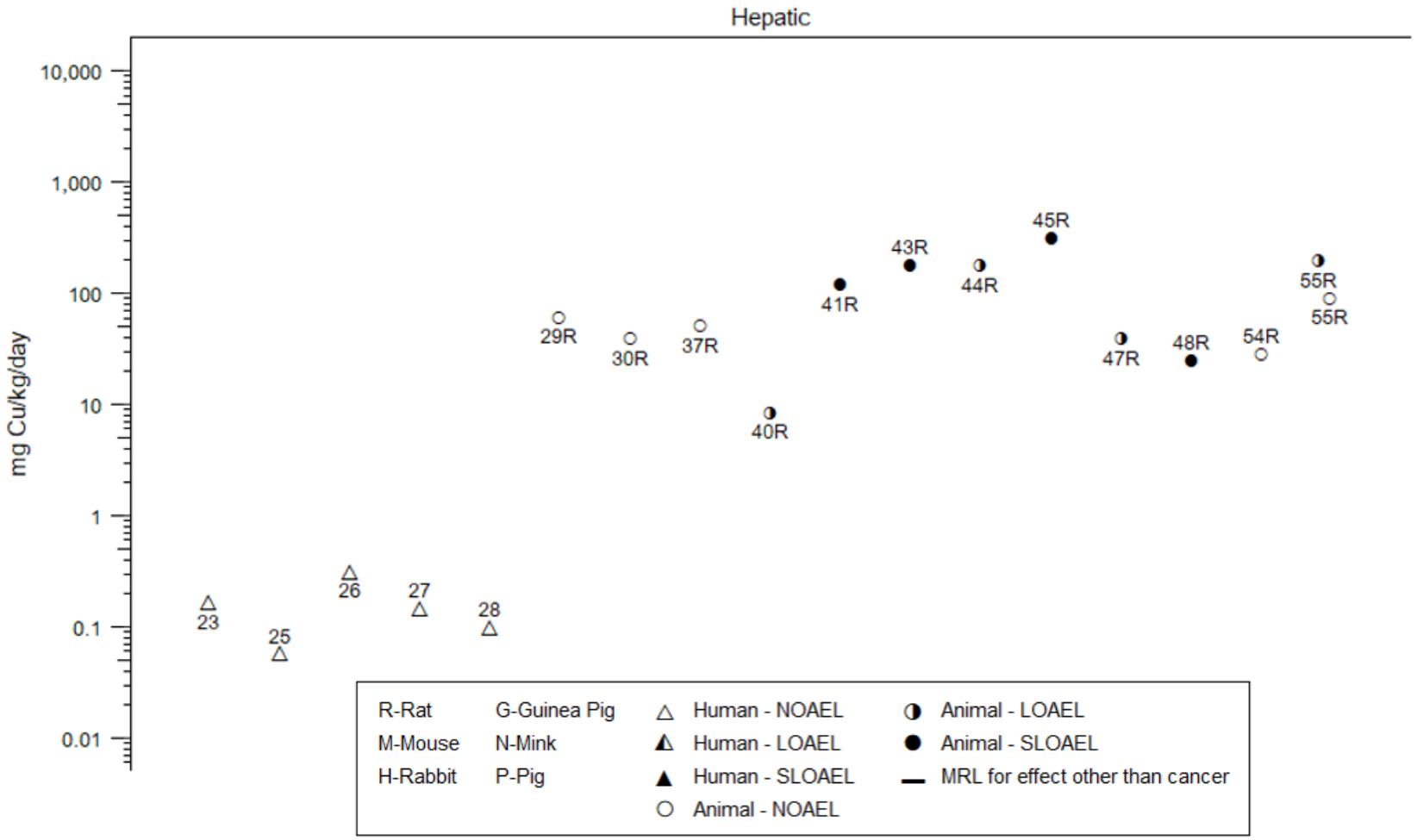


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

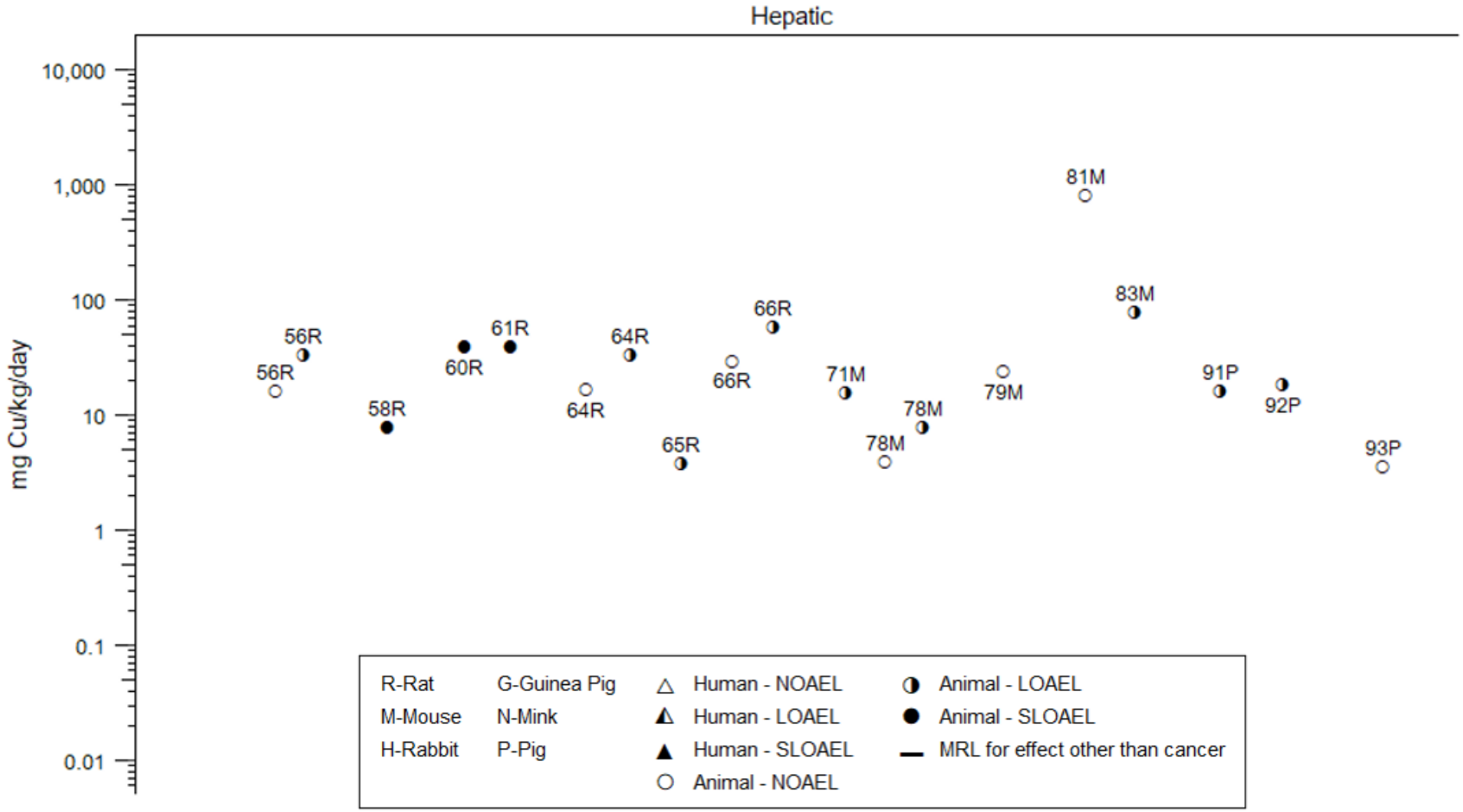


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

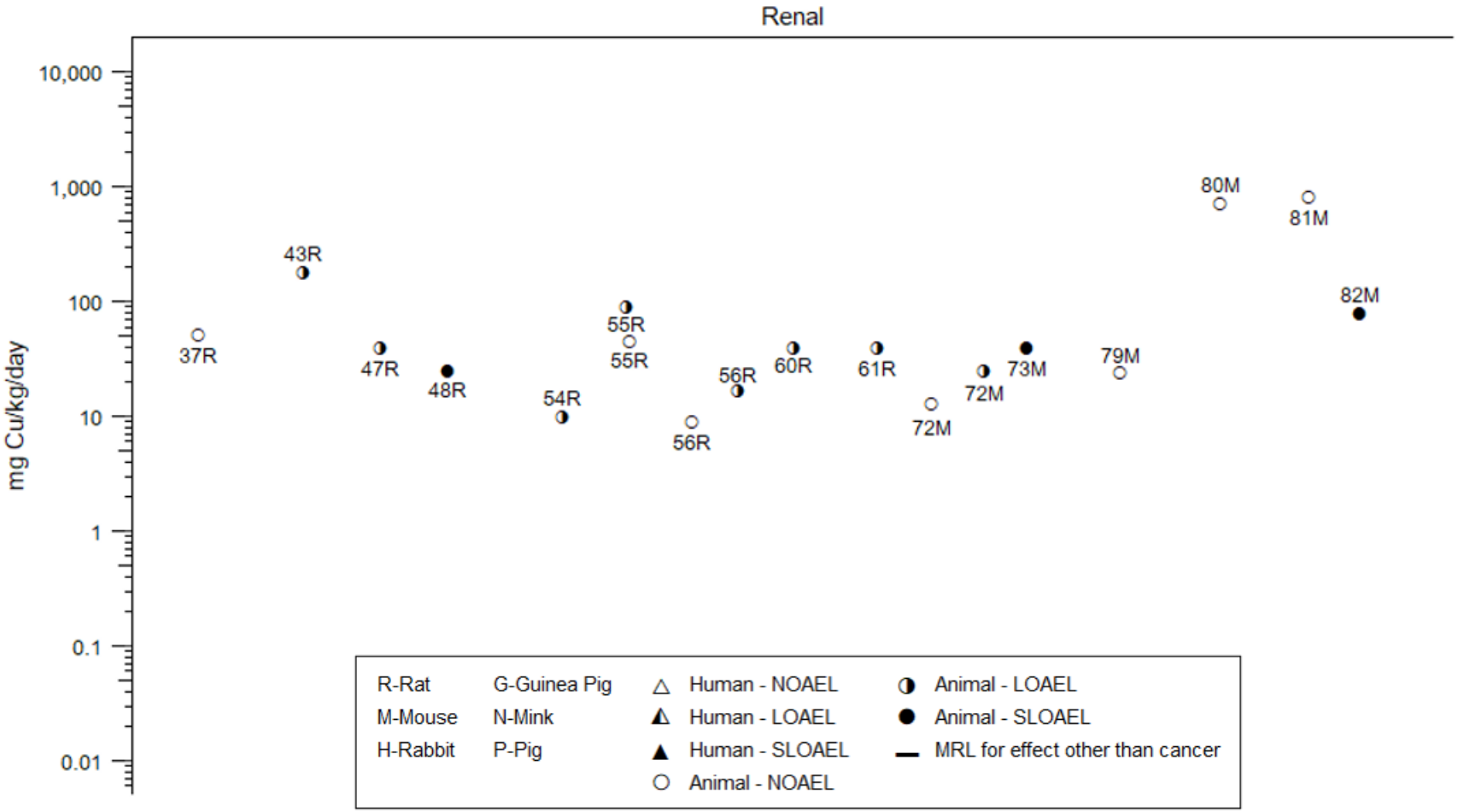


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

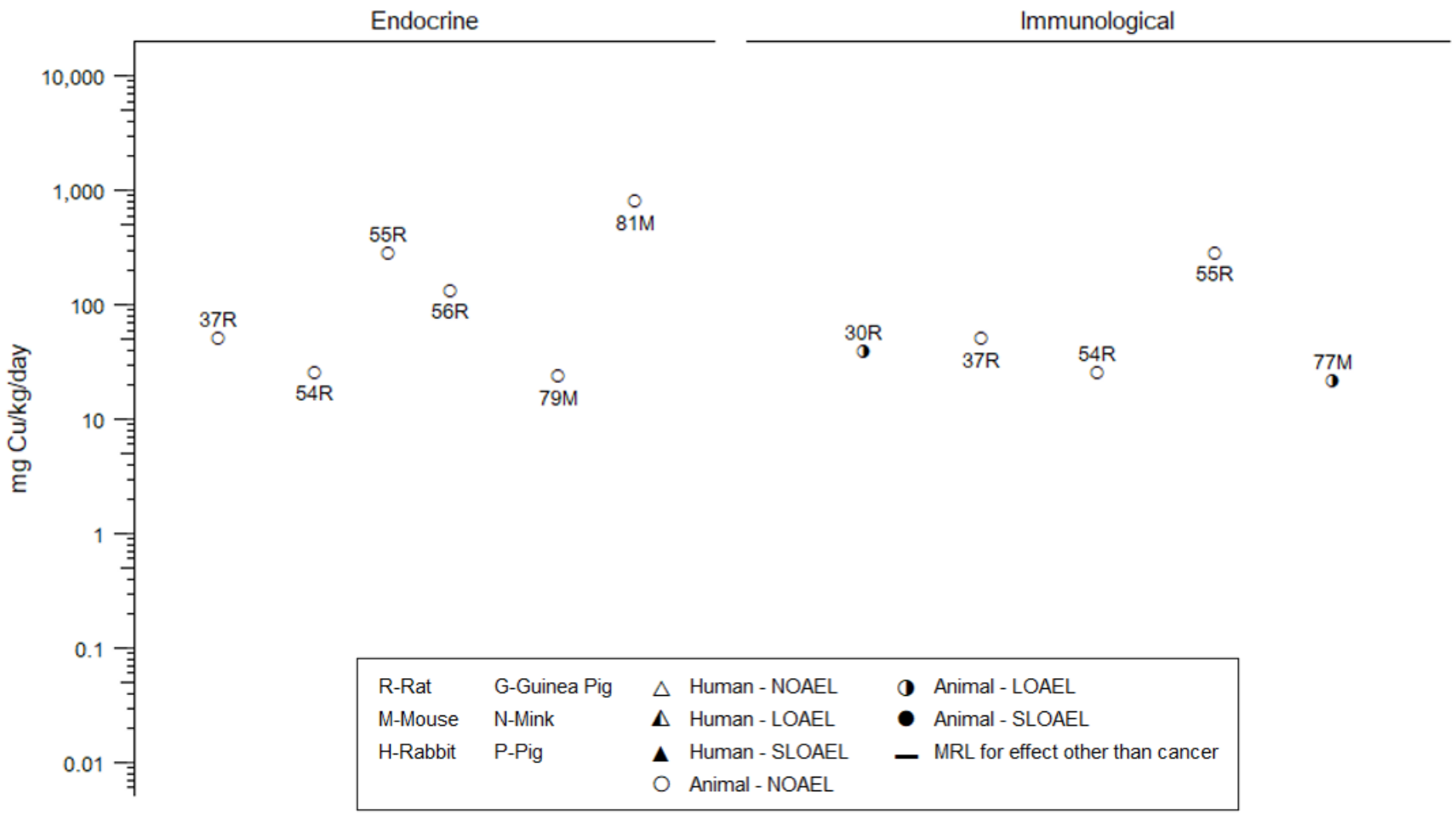


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

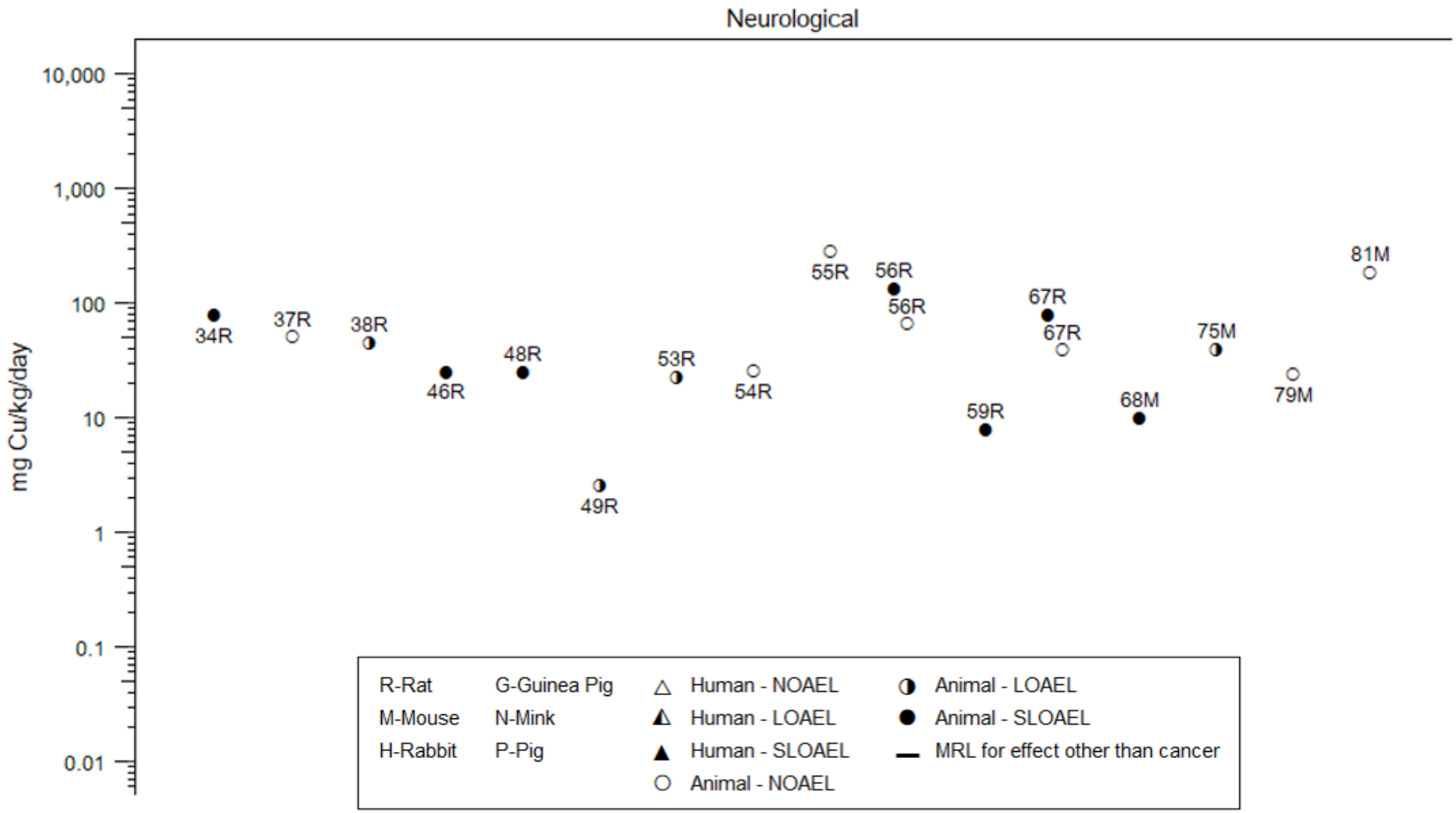


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

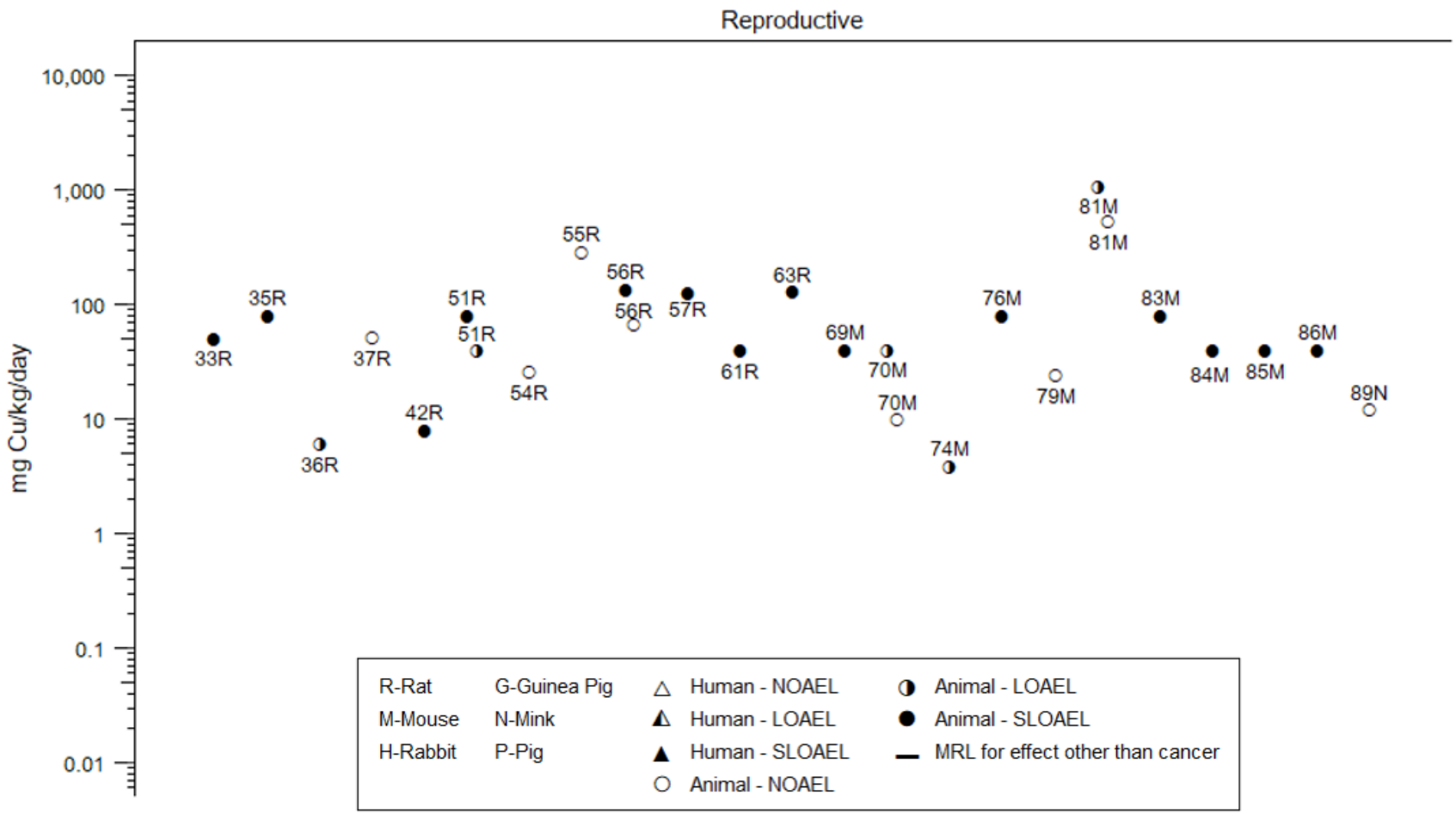


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Intermediate (15–364 days)

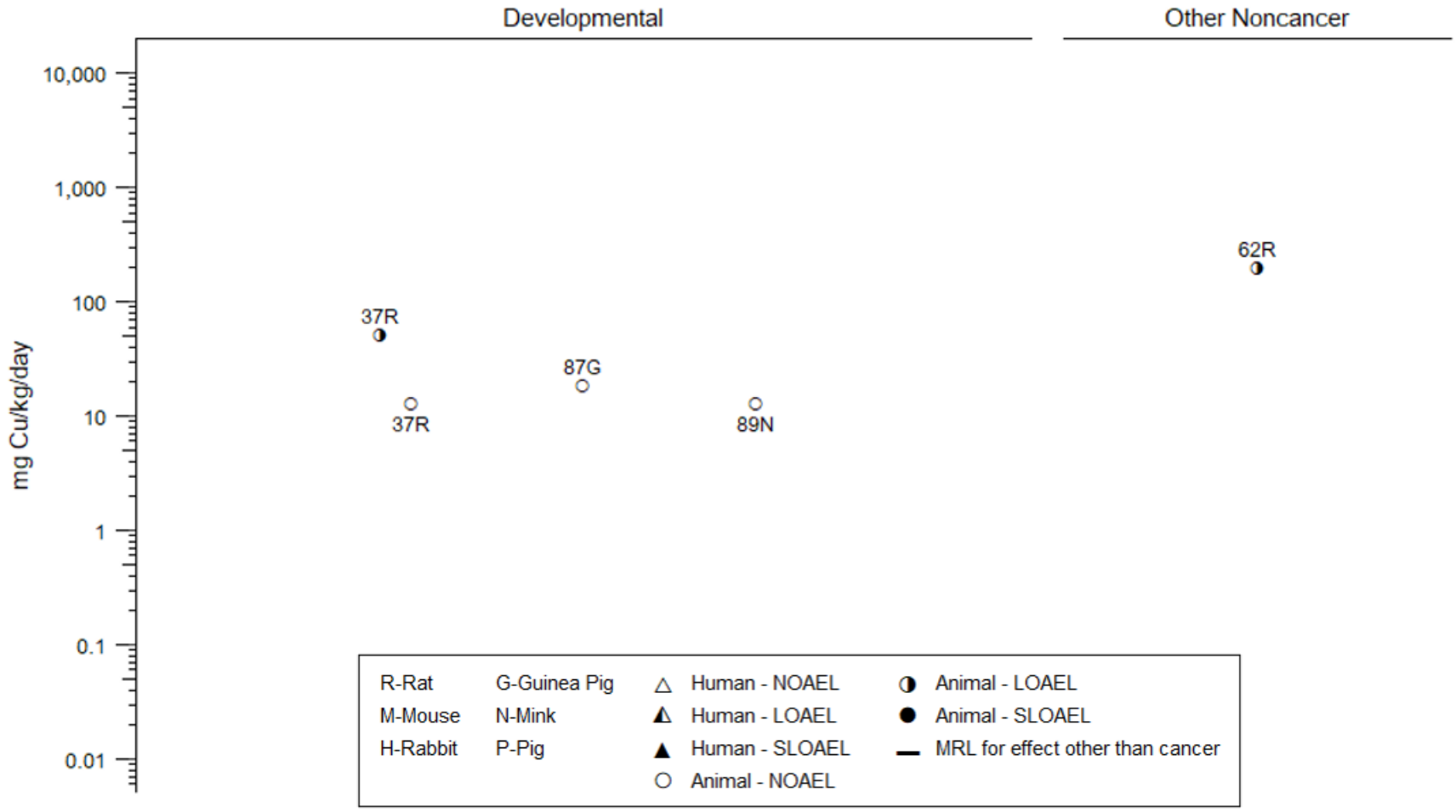
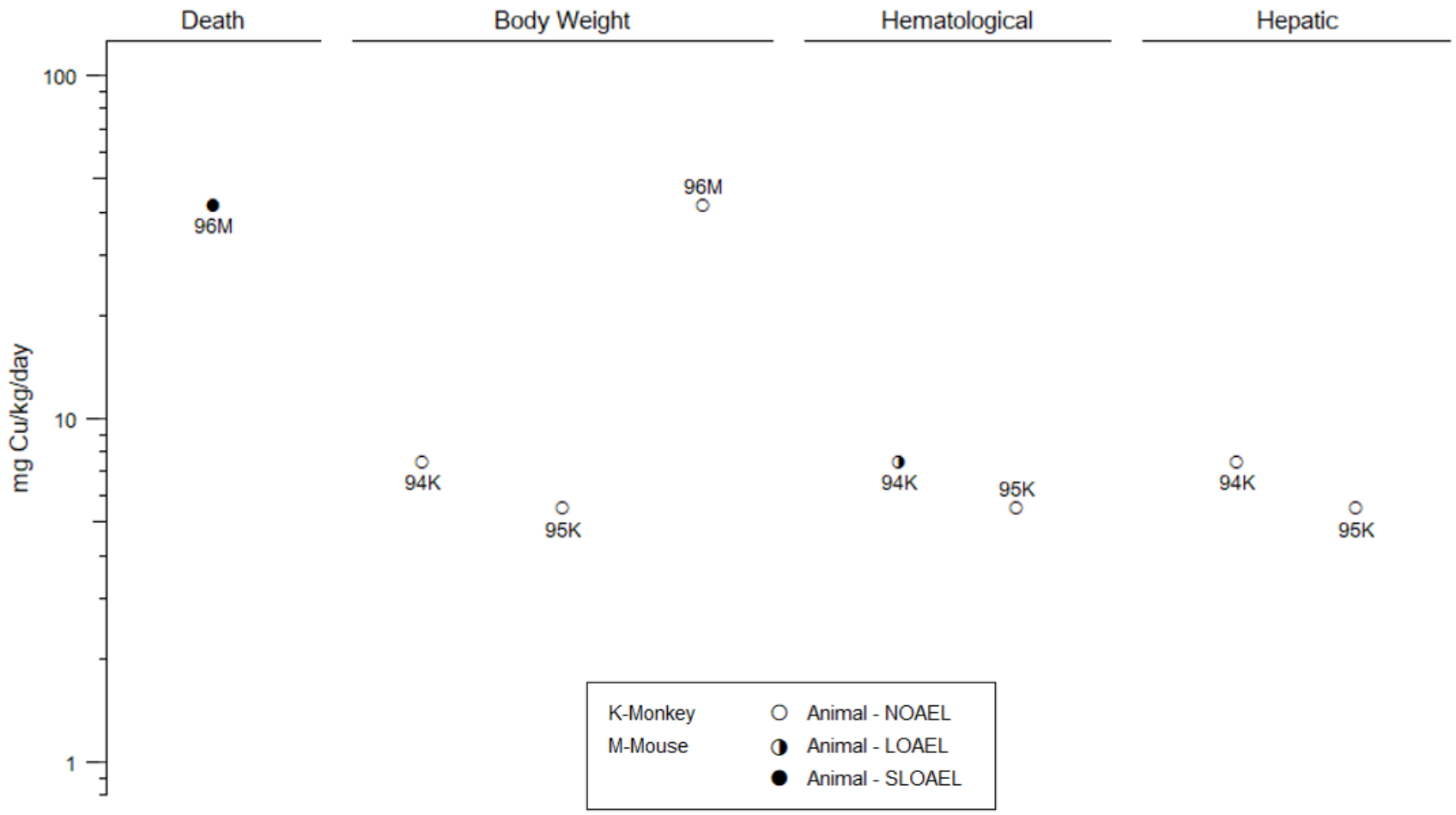


Figure 2-3. Levels of Significant Exposure to Copper – Oral
Chronic (≥365 days)



2.2 DEATH

No studies were located regarding death of humans following inhalation exposure to copper. Several case studies reported death following ingestion of large doses of copper sulfate (Chuttani et al. 1965; Griswold et al. 2017; Gupta et al. 2018; Sharma 2011). For example, death by cardiac arrest following ingestion of copper sulfate crystals was reported in two case studies: one involved a 26-year-old man who intentionally ingested an unknown amount of copper sulfate crystals, and another was a situation where a 60-year-old man accidentally ingested 15–18 mg of copper sulfate as crystals (Griswold et al. 2017; Gupta et al. 2018). In a case series, 7 of 48 individuals admitted with copper sulfate poisoning died (Chuttani et al. 1965). The deaths occurring within 24 hours of ingestion were attributed to shock, and deaths after 24 hours were likely due to hepatic and/or renal complications. Deaths, likely due to central nervous system depression and hepatic or renal failure, were also reported in individuals ingesting "spiritual green water," which contains ≥100 mg Cu sulfate/L (Akintonwa et al. 1989).

No studies were found regarding death in humans following dermal exposure to copper; however, some studies reported deaths from different exposure routes than those reported above. One case study reported death by multi-organ failure in a 22-year-old man who intentionally intravenously injected approximately 1 g copper sulfate dissolved in water into his right arm (Behera et al. 2007). Another case study reported death by hypoxia and multi-organ failure in a 29-year-old pregnant woman who intentionally exposed her vaginal tissues to an unknown amount of copper sulfate dissolved in water (Motlhatlhedi et al. 2014).

Few published data on death after inhalation exposure in animals were located. EPA's 2006 Memorandum, *Coppers: Revised human health chapter of the reregistration Eligibility Decision Document (RED) and response to comments from the Phase 3 public comment period,* reviewed a number of unpublished studies of the acute-duration inhalation lethality of copper compounds. These studies were submitted to EPA and are not in the public domain, so the only information available to ATSDR was from the secondary source; thus, these data are not included in the LSE table or figure. EPA (2006) did not report species or exposure duration for the median lethal concentration (LC_{50}) values, but the inhalation studies submitted to EPA's pesticides program are typically 4-hour rat lethality studies. The LC_{50} values reported by EPA (2006) are shown in the Table 2-3.

Table 2-3. LC_{50} Values for Copper Compounds[a] Reported by EPA (2006)

Compound	Composition information	Sex	LC_{50} (mg/m^3 compound)
Copper hydroxide	77%	Male	1,530
		Female	1,040
Copper oxychloride	94.1%	NR	>1,700
Copper, metallic	23%	NR	>100 and <590
Cupric oxide (CuO)	97.6%	Both	>2,080
Cuprous oxide/dicopper oxide (Cu_2O)	40.9% a.i.	NR	100–590
Copper 8-quinolinolate ($C_{18}H_{12}CuN_2O_2$)	96%	Both	89
KOMEEN and K-Tea (elemental copper, ethylenediamine)	NR	Male	1,360
		Female	560
Copper naphthenate	9.5% Cu	Both	>2960
Copper octanoate, 10% fatty acids	NR	Both	380
Cuprous thiocyanate	99%	NR	>500

[a]EPA (2006) did not report the species tested, but acute-duration inhalation lethality studies are typically conducted in rats and/or mice.

a.i. = active ingredient; NR = not reported

The oral median lethal dose (LD_{50}) for mice administered copper sulfate was reported as 39.8 mg Cu/kg, however, only two mice were tested per dose in an "up and down" method (Kadammattil et al. 2018). Total mortality was observed in rats fed 140 mg Cu/kg/day as copper sulfate for 1 week, compared to controls (Boyden et al. 1938). Reduced food intake, possibly the result of taste aversion, contributed to the deaths.

EPA (2006) reported oral LD_{50} values from unpublished studies of copper compounds; these values are shown in Table 2-4. As with the inhalation values, EPA (2006) did not report the species or mode of administration for these studies; however, these studies are typically conducted using rats or mice exposed by gavage. The lowest LD_{50} values were for KOMEEN and K-Tea (elemental copper, ethylenediamine) and for copper sulfate pentahydrate.

Table 2-4. Oral LD_{50} Values for Copper Compounds Reported by EPA (2006)[a]

Compound	Composition information	Sex	LD_{50} (mg/kg compound)
Copper chloride	57.7%	Male	1,796
		Female	2,006
Copper carbonate	96%	NR	>2,000

Table 2-4. Oral LD_{50} Values for Copper Compounds Reported by EPA (2006)[a]

Compound	Composition information	Sex	LD_{50} (mg/kg compound)
Copper hydroxide	77%	Male	2,253
		Female	2,160
Copper oxychloride	94.1%	Male	1,537
		Female	1,370
Copper sulfate pentahydrate	99%	Male	790
		Female	450
Copper, metallic	50%	Male	1,414
		Female	1,625
Cupric oxide	97.6%	Both	>5,050
Cuprous oxide	57%.	NR	>5,000
Copper 8-quinolinolate	99.5%	Both	>5,000
Copper from triethanolamine complex (K-Tea)	99%	Male	1,170
		Female	1,312
KOMEEN and K-Tea (elemental copper, ethylenediamine)	KOMEEN 96%, K-Tea 99%	Male	527
		Female	462
Copper naphthenate	8% Cu	Both	>5,050
Copper octanoate, 10% fatty acids	NR	Both	>2,000
Copper salts of fatty and rosin acids (Cu and zinc neoisoate 35%)	NR	NR	>7,000
Cuprous thiocyanate	99%	NR	>5,000

[a]EPA (2006) did not report the species tested, but most acute-duration oral lethality studies are typically conducted in rats and/or mice.

NR = not reported

Intermediate-duration animal studies reported deaths from oral exposure to copper in drinking water and via gavage, but not when administered in food. In drinking water studies, all rats died or were sacrificed moribund when groups of five male and five female rats orally exposed to ≥36 and 31 mg Cu/kg/day, respectively, as copper sulfate pentahydrate in water for 15 days (NTP 1993). Similar results were seen in mice. One of five male mice and three of five female mice died following exposure to 57 and 62 mg Cu/kg/day, and all mice died at higher doses when copper sulfate pentahydrate was administered in water for 15 days (NTP 1993). In both rats and mice exposed via the drinking water, there were profound decreases in water consumption at the higher doses, which NTP (1993) attributed to palatability. As a result, the animals were dehydrated, which may have contributed to the mortalities.

Two of 12 rats died following exposure to 51 mg Cu/kg/day as copper chloride via gavage for up to 38 days in a combined repeat-dose and reproductive/developmental toxicity screening study (Chung et al. 2009). No deaths were reported in rats or mice receiving doses up to 324 or 717–781 mg Cu/kg/day, respectively, as copper sulfate pentahydrate in food for 15 days. In 13-week studies, no mortality was reported in male or female rats exposed daily to 140 or 134 mg Cu/kg/day (respectively) or in male or female mice exposed to 815 or 1,058 mg Cu/kg/day (respectively) as copper sulfate pentahydrate in feed (NTP 1993). NTP (1993) did not conduct 13-week studies using drinking water administration due to the premature deaths seen in the 15-day studies.

In an unpublished developmental toxicity study submitted to EPA and reviewed by EPA (2006), doses of 18 mg Cu/kg/day as copper hydroxide administered via gavage over gestation days (GDs) 7–28 resulted in death in 3/22 pregnant New Zealand White rabbits. No deaths were reported at 9 mg Cu/kg/day (reviewed by EPA 2006).

Chronic-duration oral studies in animals were limited. Lifetime exposure of mice to 42 mg Cu/kg/day as copper gluconate in drinking water resulted in an average 12.8% reduction of the maximum lifespan (from 986 to 874 days) and an average 14.4% decrease in their mean survival time (Massie and Aiello 1984).

Dermal LD_{50} values reported by EPA (2006) for copper compounds are shown in Table 2-5; species was not reported in the secondary source, but these studies generally use rats or rabbits. Only copper oxychloride had a dermal LD_{50} value below the upper limit dose of 2,000 mg compound/kg used in these studies.

Table 2-5. Dermal LD_{50} Values for Copper Compounds Reported by EPA (2006)[a]

Compound	Composition information	Sex	LD_{50} (mg/kg as compound)
Copper chloride	57.7%	Both	>2,000
Copper hydroxide	77%	NR	>2,000
Copper oxychloride	94.1%	Both	710
Copper sulfate pentahydrate	99%	NR	>2,000
Copper, metallic	8.5% elemental	NR	>2,000
Cupric oxide	97.6%	Both	>2,020
Cuprous oxide	57%	NR	>2,000
Copper 8-quinolinolate	99.5%	Both	>2,000

Table 2-5. Dermal LD_{50} Values for Copper Compounds Reported by EPA (2006)[a]

Compound	Composition information	Sex	LD_{50} (mg/kg as compound)
Copper from triethanolamine complex (K-Tea)	99%	NR	>2,000
KOMEEN and K-Tea (elemental copper, ethylenediamine)		NR	>2,000
Copper naphthenate	8% Cu	Both	>2,020
Copper octanoate, 10% fatty acids		Both	>2,000
Copper salts of fatty and rosin acids (copper and zinc neoisoate 35%)		NR	>2,000
Cuprous thiocyanate	99%	NR	>2,000

[a]EPA (2006) did not report the species tested, but most acute-duration dermal lethality studies are typically conducted in rats and/or rabbits.

NR = not reported

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following inhalation exposure to copper or in humans exposed dermally. No effects on body weight were observed in a controlled exposure study in women exposed to a daily dose of up to 0.1 mg Cu/kg/day as copper sulfate for 2 weeks (Pizarro et al. 1999). In addition, no changes in body weight were reported in infants given daily doses up to 0.319 mg Cu/kg/day as copper sulfate in drinking water for 9 months (Olivares et al. 1998).

Only one study of body weight in animals exposed to copper via inhalation was located. No effects on body weight were observed in rats exposed to 8.9 mg Cu/m^3 as dicopper oxide for 6 hours/day, 5 days/week, for 2 weeks (6 hours/day) or to 1.76 mg Cu/m^3 for 6 hours/day, 5 days/week, for 4 weeks (Poland et al. 2022). In a companion study of copper sulfate pentahydrate in the same publication, male body weights were significantly decreased on day 4 (10.3%) and day 11 (13.8%) in the 8.9 mg Cu/m^3 group (Poland et al. 2022). These body weight decreases were accompanied by decreased food intake, but the study authors did not report food intakes, so it is difficult to establish whether the body weight effects were attributable to the decline in food consumption.

In an acute-duration oral study, a decrease in terminal body weight of 28% was observed in mice exposed to 6.4 mg Cu/kg/day as copper sulfate pentahydrate via gavage for 14 days (Al-musawi et al. 2022).

Intermediate-duration studies had mixed results on body weight changes. Intermediate-duration oral exposure studies to copper sulfate reported 10–28% decreases of body weight and 12–51% decreases in body weight gain in rats following exposure to as little as 12 mg Cu/kg/day for 15–91 days (Chen et al. 2023; Haywood and Loughran 1985; Kumar and Sharma 1987; Kumar et al. 2015, 2016a, 2016b; Rana and Kumar 1980); in mice following exposure to as low as 4 mg Cu/kg/day for 15–133 days (Dai et al. 2023; Kvietkauskaite et al. 2004; Liu et al. 2021c); and in pigs following exposure to 2.3 mg Cu/kg/day for 88 days (Kline et al. 1971). Rats exposed to 160 mg Cu/kg/day as tribasic copper chloride for 12 weeks exhibited decreased terminal body weights by 11% (Yu et al. 2023). Significant decreases in body weight were reported in rats exposed to 39.8 mg Cu/kg/day as copper sulfate for 90 days, but were not further described (Kumar et al. 2016a, 2016b). Decreased body weight gains (22–27%) were observed in pigs following exposure to 16.5–18.7 mg Cu/kg/day as copper carbonate for 46–49 days (Suttle and Mills 1966). A 78% decrease in body weight gain was observed in mice exposed via gavage to 16 mg Cu/kg/day as copper sulfate for 20 days (Dab et al. 2023). A 17% decrease in body weight gain was observed in pigs exposed to 2.3 mg Cu/kg/day as copper sulfate for 88 days; no effects were observed at 1.7 mg Cu/kg/day (Kline et al. 1971). Decreased body weight gains of 23% were observed in rats following exposure to 120 mg Cu/kg/day as copper acetate for 21 weeks (Llewellyn et al. 1985).

NTP (1993) evaluated a comprehensive set of toxicological endpoints including body weight effects in rats and mice exposed to copper sulfate pentahydrate in water or diet for 15 days or 13 weeks. In the 15-day studies, male rats fed 198 mg Cu/kg/day exhibited an 18% decrease in body weights, with no effects observed at 92 mg Cu/kg/day, while female rats fed 285 mg Cu/kg/day exhibited a 13% decrease in body weights, with no effects observed at 196 mg Cu/kg/day. Male and female rats had reduced food intake in these studies, at a range of 37–8%, thus confounding the decrease in body weights and reducing the compound intake. Mice fed up to 780 mg Cu/kg/day had no body weight effects. Rats given 31–36 mg Cu/kg/day in the drinking water had decreased body weights by 48% in males and 46% in females, while doses of up to 29 mg Cu/kg/day in the drinking water for 15 days had no effect on body weights. Mice had 22–34% decreases in body weights when administered 57–62 mg Cu/kg/day in water for 15 days, but no effects were observed at 24–36 mg Cu/kg/day. Due to high toxicity at the highest two doses in drinking water, changes in mice body weight were only observed at the mid dose. The drinking water studies were also confounded by decreased water consumption resulting in dehydration in the animals; therefore, no 13-week drinking water studies were performed. In the 13-week studies by NTP (1993), male rats fed 140 mg Cu/kg/day had a 24% decrease in body weight. No effects on body weights were observed in male rats fed 66 mg Cu/kg/day or in female rats fed 134 mg Cu/kg/day. In mice, males and females, respectively, fed 187 and 536 mg Cu/kg/day had 10 and 12% decreases in body weight. No

effects on body weights were observed in male mice at 97 mg Cu/kg/day or in female mice at 267 mg Cu/kg/day.

Numerous studies reported no effects on body weight in intermediate-duration studies in animals exposed to copper sulfate or copper sulfate pentahydrate at doses up to 50.9 mg Cu/kg/day in rats (Adele et al. 2023; Gupta et al. 2021; Kalita et al. 2020; Khushboo et al. 2018; Kumar et al. 2019; Patwa and Flora 2020; Seven et al. 2018), up to 50.9 mg Cu/kg/day in mice (Dai et al. 2020), up to 18.4 mg Cu/kg/day in guinea pigs (Seffner et al. 1997), and at 3.62 mg Cu/kg/day in pigs (Zhang et al. 2020). No changes in body weights were observed in rats given 62 mg Cu/kg/day as copper gluconate for 6 weeks (Abe et al. 2008) or in rats exposed to 51 mg Cu/kg/day as copper chloride for ~35 days (Chung et al. 2009). No changes in body weights were exhibited in mice exposed to 8.6 mg Cu/kg/day as copper acetate (Epstein et al. 1982).

A chronic-duration study (through the lifespan) found no biologically significant body weight effects in mice exposed to 42 mg Cu/kg/day as copper gluconate in drinking water (Massie and Aiello 1984). A 2-year study in monkeys also found no effects on body weight following exposure to doses of 5.5–7.5 mg Cu/kg/day as copper gluconate delivered to animals in food or milk (Araya et al. 2012).

2.4 RESPIRATORY

In humans, airborne copper particles are respiratory irritants. Workers exposed to copper dust have reported symptoms such as coughing, sneezing, thoracic pain, and runny nose (Askergren and Mellgren 1975; Suciu et al. 1981). In an occupational study of 75–100 workers involved with sieving copper dust, lung radiographs revealed linear pulmonary fibrosis, and in some cases, nodulation (Suciu et al. 1981). The study authors noted that “the workers employed on sieving the copper dust were exposed to a 99.9011% purity of copper.” During the first year of operation, the workers were exposed to an estimated average concentration of 464 mg Cu/m^3; the exposure levels declined each year due and by the third year, the levels were estimated to average 111 mg Cu/m^3 (Suciu et al. 1981). Suciu et al. (1981) did not include a comparison group, so the findings are difficult to interpret. Among sheet metal workers exposed to patina dust (copper-hydroxide-nitrate, copper-hydroxide-sulfate, copper silicate, copper oxide), 6 of the 11 examined workers displayed increased vascularity and superficial epistatic vessels in the nasal mucosa (Askergren and Mellgren 1975); however, copper exposure levels were not reported.

Epidemiological studies of respiratory effects in humans exposed to airborne copper are summarized in Table 2-6. Automotive workers in Iran who were exposed to copper particles from welding reported symptoms of cough, sputum, and wheezing (Saadiani et al. 2023). In this study, exposure to copper in the welding unit (mean concentration 0.107 mg Cu/m^3) was also associated with decreased forced expiratory volume in 1 second (FEV_1). The workers had co-exposure to other heavy metals (lead and iron) and the analyses did not adjust for these co-exposures. Two studies evaluated respiratory effects in workers at secondary copper smelters in Egypt, where coexposures included arsenic, lead, and cadmium (Fouad and Ramadan 2022; Mourad and El-Sherif 2022). These studies did not account for co-exposures. Compared to administrative workers without metal dust exposure, workers exhibited higher prevalence of symptoms of respiratory irritation (cough, expectoration, nasal irritation) and reduced respiratory function as measured by spirometry (Fouad and Ramadan 2022; Mourad and El-Sherif 2022). Chest x-rays showed a significant difference in the prevalence of radiological infiltrates (primarily reticular infiltrations) between the smelter workers (36%) and administrative workers (4%) (Fouad and Ramadan 2022). Copper concentrations in air were not measured or reported in either study of copper smelter workers; however, serum copper concentrations were higher in the exposed groups than the referents, supporting a difference in exposure levels.

Table 2-6. Results of Selected Epidemiological Studies Evaluating Exposure to Copper and Respiratory Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Saadiani et al. 2023 Cross-sectional, 1,152 automotive welders and 1,152 administrative staff (mean ages 37.5 and 38.5 years, respectively); welders were exposed to copper, lead, and iron (Iran)	Work in welding unit	Cough, sputum, and wheezing prevalence	↑
	Average air concentration in welding unit: 0.107 mg Cu/m^3	FEV_1	↓
Fouad and Ramadan 2022 Cross-sectional, 75 male copper smelter workers and 75 male administrative workers (mean ages 43.19 and 44.05 years, respectively); workers were exposed to copper and arsenic (Egypt)	Work in smelter operations; mean serum copper was 191.41 µg Cu/dL in exposed and 137.30 µg Cu/dL in controls	Prevalence of nasal irritation, rhinitis, sinusitis, cough, expectoration, wheeze, dyspnea	↑
		Prevalence of radiological infiltrates on chest x-ray	↔
		FVC, FEV_1, FEV_1/FVC, PEF, FEF_{25}, FEF_{50}, FEF_{75}	↓

Table 2-6. Results of Selected Epidemiological Studies Evaluating Exposure to Copper and Respiratory Effects

Reference, study type, and population	Exposure concentration	Outcome evaluated	Result
Mourad and El-Sherif 2022 Cross-sectional, 65 male copper smelter workers and 41 matched male administrative workers (mean ages 43.19 and 44.05 years, respectively); workers were exposed to copper, arsenic, lead, and cadmium (Egypt)	Work in smelter operations; mean serum copper was 175.2 µg Cu/dL in exposed and 93.44 µg Cu/dL in controls	Prevalence of exertional dyspnea, cough, expectoration	↑
Boogaard et al. 2013 Cohort study; 661 individuals (at least 4 years of age) in 12 locations, evaluated before and after implementation of traffic reduction policies (Netherlands)	Decrease in mean concentration in ambient air from 2008 to 2010: 27.2 ng Cu/m^3	FVC change between 2008 and 2010	↑ (improved)
Yu et al. 2021b Prospective cohort study; 706 adolescents in PIAMA birth cohort (47.3% male); respiratory symptoms and spirometry evaluated at 13–16 years of age (Netherlands)	Modeled concentration in ambient air at current residence 2.6 ng Cu/m^3 (mean in $PM_{2.5}$) 11 ng Cu/m^3 (mean in PM_{10})	FEV_1, FVC at age 13–16 years	↔
Gehring et al. 2015 Prospective cohort study; 3,702 participants in PIAMA birth cohort (52% male); respiratory symptoms and spirometry evaluated at 8 and 11–12 years of age (Netherlands)	Modeled concentration in ambient air at birth address: 3.1 ng Cu/m^3 (mean in $PM_{2.5}$) 12.8 ng Cu/m^3 (mean in PM_{10})	FEV_1	↓ for Cu in $PM_{2.5}$ at current address
		$FEF_{25–75}$	↓ for Cu in PM_{10} at current address
		FVC	↔

↑ = association; ↓ = inverse association; ↔ = no association; FEF_{25} = forced expiratory flow at 25% of the pulmonary volume; FEF_{50} = forced expiratory flow at 50% of the pulmonary volume; FEF_{75} = forced expiratory flow at 75% of the pulmonary volume; $FEF_{25–75}$ = forced expiratory flow at 25–75% of the pulmonary volume; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; PIAMA = Prevention and Incidence of Asthma and Mite Allergy; $PM_{2.5}$ = particulate matter ≤2.5 µm; PM_{10} = particulate matter ≤10 µm

Copper was considered the etiologic agent in an occupational disorder referred to as "vineyard sprayer's lung." This condition was found in vineyard workers that used an anti-mildew agent known as the "Bordeaux mixture" that contains 1– 2.5% copper sulfate (with pH neutralized via hydrated lime) (Pimentel and Marques 1969). Published information on this disorder is primarily from case reports

(Pimentel and Marques 1969; Pimentel and Menezes 1975; Stark 1981; Villar 1974; Villar and Nogueira 1980) that lacked quantitative exposure information. Alveolar lavage and biopsy findings consisted of interalveolar desquamation of macrophages, formation of histiocytic and noncaseating granulomas containing inclusions of copper, and healing of lesions in the form of fibrohyaline nodules. These lesions are very similar to those found in silicosis (Pimentel and Marques 1969; Plamenac et al. 1985). Higher incidences of abnormal columnar cells, squamous metaplasia without atypia, copper-containing macrophages, eosinophilia, and respiratory spirals were found in the sputa of smoking and nonsmoking vineyard sprayers, and not in rural workers from the same geographic region who did not work in the vineyards (Plamenac et al. 1985).

A few epidemiological studies evaluated respiratory effects of exposure to copper in particulate matter in ambient air (see Table 2-6). A decline of copper concentration in particulate matter was associated with improved forced vital capacity (FVC) in 661 subjects in a cohort study in the Netherlands (Boogaard et al. 2013). In two studies of the same birth cohort, spirometry measures showed inconsistent relationships to copper concentration in particulate matter. When measured at ages 8 and 11–12 years, FEV_1 was inversely associated with copper concentration in $PM_{2.5}$ (particulate matter ≤2.5 μm) at the child's current home address and $FEF_{25–75}$ (forced expiratory flow at 25–75% of the pulmonary volume) was inversely associated with copper concentrations in PM_{10} (particulate matter ≤2.5 μm) (Gehring et al. 2015). When the children were evaluated during adolescence (ages 13–16 years), spirometry measures were not associated with copper concentration in $PM_{2.5}$ or PM_{10} at the child's current residence.

Several case studies reported respiratory effects in humans following both accidental and intentional ingestion of copper sulfate crystals, powder, or liquid; the most common effects are tachypnea (fast breathing) and dyspnea (labored breathing) (Cho et al. 2018; Franchitto et al. 2008; Gunay et al. 2006; Gupta et al. 2018; Hassan et al. 2010; Higny et al. 2014; Sinkovic et al. 2008; Sood and Verma 2011; Yang et al. 2004). Aspiration pneumonia was reported in two cases of intentional copper sulfate ingestion, one in a 45-year-old man and one in a 29-year-old man (Franchitto et al. 2008; Gamakaranage et al. 2011). Diffuse bilateral infiltration of the lungs was observed in a 44-year-old man who intentionally ingested >100 g copper sulfate (Cho et al. 2018).

Respiratory effects were also documented in case reports of exposure to copper by other routes. A 2-year-old female child developed an acute respiratory distress syndrome with cyanosis, dyspnea, bilateral hyperinflation, and interstitial infiltrates of the lungs following inhalation of copper dust (Donoso et al. 2007). A 24-year-old man developed a deviated septum with persistent sinus pressure and

rhinorrhea after spilling molten copper on his face shield; inhalation of the associated fumes was suggested as a contributing factor (Gibson et al. 2011). A 40-year-old woman developed acute respiratory distress syndrome after intentionally inserting an unknown amount of copper sulfate into her rectum (Moussiegt et al. 2020). A 41-year-old woman developed respiratory failure with bi-basal pneumonia after intentionally injecting 2.5 g copper glycinate subcutaneously (Oon et al. 2006).

The potential for copper to induce respiratory effects has been evaluated in acute-duration studies in rats, mice, and hamsters, as well as in intermediate-duration studies in rats and rabbits.

Drummond et al. (1986) compared respiratory effects in mice and hamsters after single and repeated 3-hour inhalation exposures to several sulfate compounds including copper sulfate. The study authors reported exposure concentrations in terms of sulfate (0.09, 0.1, 0.43, 0.93, and 2.53 mg SO_4/m^3) and in terms of "calculated mg metal/m^3" (reporting values of 0.12, 0.13, 0.56, 1.21, and 3.3 mg metal/m^3, respectively). However, the reported copper concentrations are inconsistent with the concentrations reported in terms of sulfate[1]. Because of the error, the copper exposure concentrations are uncertain and effect levels cannot be determined for the study. Drummond et al. (1986) reported decreased cilia beating frequency and a decreased percentage of normal epithelium in tracheal explants from Syrian-Golden hamsters, but not CD-1 mice, after a 3-hour exposure to copper sulfate. However, after repeated 3-hour exposures to the lowest concentrations of copper sulfate, mice exhibited increased alveolar wall thickening. The severity of the effect increased with the duration of exposure, and was characterized as "extensive" after 10 exposures (Drummond et al. 1986). Pulmonary histology was not assessed in hamsters after single or repeated exposures (Drummond et al. 1986).

Poland et al. (2022) compared the respiratory effects of dicopper oxide and copper sulfate pentahydrate particles in rats exposed by inhalation for 2 weeks at identical copper concentrations of 0, 0.18, 0.71, 1.78, and 8.9 mg Cu/m^3. The results showed that copper sulfate pentahydrate induced respiratory effects at a slightly lower copper exposure level than dicopper oxide, but both compounds induced the same kinds of effects. Both male and female rats exhibited alveolar histiocytosis and males showed bronchioloalveolar hyperplasia after exposure to 0.71 mg Cu/m^3 as copper sulfate pentahydrate. Rats of

[1]For example, Drummond et al. (1986) reported one copper sulfate exposure level as 2.53 mg SO_4/m^3 and 3.3 "mg metal/m^3." However, the copper concentration (from copper sulfate) corresponding to 2.53 mg SO_4/m^3 would be 1.67 mg Cu/m^3 (calculated as mg SO_4 x (molecular weight of copper/molecular weight of sulfate). Copper concentrations based on the reported sulfate concentrations of 0.09, 0.1, 0.43, 0.93, and 2.53 mg SO_4/m^3 would be 0.06, 0.07, 0.28, 0.62, and 1.67 mg Cu/m^3, respectively. This apparent error was limited to the copper concentrations, as the aluminum concentrations reported as "mg metal/m^3" for exposures to aluminum sulfate compounds in the study were consistent with the corresponding sulfate concentrations.

both sexes exhibited markedly increased absolute and relative lung weights (≥69% relative to controls) at ≥1.78 mg Cu/m^3 as copper sulfate pentahydrate. In contrast, neither male nor female rats exhibited respiratory effects at 0.71 mg Cu/m^3 as dicopper oxide. At 1.78 mg Cu/m^3 as dicopper oxide, rats of both sexes showed alveolar histiocytosis and females had increased absolute and relative lung weights (28 and 25%, respectively, compared with controls). Significant increases in absolute and relative lung weights (65 and 62%, respectively) were only seen in males at 8.9 mg Cu/m^3 as dicopper oxide (Poland et al. 2022). Rats exposed to both compounds showed acute neutrophilic inflammation in the lungs and degeneration of the olfactory epithelium in the nose at ≥1.78 mg Cu/m^3 (Poland et al. 2022).

In a 4-week follow up study of dicopper oxide (Poland et al. 2022), pulmonary effects in exposed rats were similar to those seen in the shorter-term experiments described above. Observed effects included exposure-related increases in absolute and relative lung weights and in severity of alveolar histiocytosis and neutrophilic inflammation in the lungs at concentrations ≥0.35 mg Cu/m^3. Minimal to mild lymphocyte infiltration was also seen in the nasal passages of males at the highest tested exposure concentration (1.76 mg Cu/m^3). Respiratory tract inflammation was also evident from BALF analyses that showed increases in neutrophils, total protein, and lactate dehydrogenase (LDH) at the same concentrations (Poland et al. 2022). In rabbits (strain not reported) exposed to 0.6 mg Cu/m^3 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 that was not considered adverse (Johansson et al. 1984). No functional (e.g., phagocytic or bactericidal activity) or morphological (as visualized by transmission and scanning electron microscopy) alterations were observed in the alveolar macrophages of similarly exposed rabbits (Johansson et al. 1983).

Data on the potential of copper to induce respiratory effects after oral exposure in experimental animals are limited to a few studies. NTP (1993) found no histological alterations in the lungs of rats orally exposed to 29–325 mg Cu/kg/day as copper sulfate in the diet for 15 or 90 days, respectively, or in mice exposed to 24 or 1,058 mg Cu/kg/day for 15 or 90 days, respectively.

In an unpublished developmental toxicity study reviewed by EPA (2006), one of three pregnant rabbits that died prematurely during gestational exposure to 18 mg Cu/kg/day (as copper hydroxide via gavage) exhibited irregular respiration. At necropsy, all three rabbits exhibited brown liquid in the chest cavity and dark discoloration and/or mottling of lung tissue (reviewed by EPA 2006).

2.5 CARDIOVASCULAR

Human data on cardiovascular effects from exposure to copper are limited. Suciu et al. (1981) compared the health outcomes of workers involved in the grinding and sieving copper dust in 1970 when concentrations in air were high (up to 464 mg Cu/m^3) to the outcomes of workers later when air concentrations were lower (≤111 mg Cu/m^3 in 1972). Among workers exposed in 1970, 16% showed arterial hypertension. In contrast 6% of workers in 1973 had arterial hypertension and palpitations. However, the findings from this study are limited because other factors that could have impacted the cardiovascular system were not reported (Suciu et al. 1981). In a cross-sectional study comparing copper smelter workers exposed to dusts containing copper, arsenic, lead, and cadmium with unexposed administrative workers, exposure in the smelter operations was associated with higher blood pressure and heart rate (Mourad and El-Sherif 2022).

Two cohort studies examined the association between modeled concentrations of copper in ambient air particulate matter and cardiovascular outcomes (Ostro et al. 2015; Peralta et al. 2021) (see Table 2-7). Ostro et al. (2015) observed an association between increased mortality from ischemic heart disease in a cohort of 101,884 current and former female teachers and administrators and increased copper concentration in particulate matter. In a cohort study of older men in Massachusetts (Peralta et al. 2021), copper concentrations in $PM_{2.5}$ were associated with decreased (improved) heart-rate corrected QT interval (prolongation of the QT interval can lead to life-threatening ventricular tachycardia).

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Copper and Cardiovascular Effects

Reference, study type, and population	Exposure	Outcome evaluated	Result
Mourad and El-Sherif 2022 Cross-sectional, 65 male copper smelter workers and 41 matched male administrative workers (mean ages 43.19 and 44.05 years, respectively); workers were exposed to copper, arsenic, lead, and cadmium (Egypt)	Work in smelter operations; mean serum copper was 175.2 µg Cu/dL in exposed and 93.44 µg Cu/dL in controls	Blood pressure and heart rate	↑

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Copper and Cardiovascular Effects

Reference, study type, and population	Exposure	Outcome evaluated	Result
Ostro et al. 2015 Prospective cohort study; 101,884 current and former female teachers and administrators in California (mean age 57.3 years), followed from 2001 to 2007 (United States); exposure modeled for each subject's residence	Modeled concentration in ambient air: 0.5 µg Cu/m^3 (mean in $PM_{2.5}$); 0.03 µg Cu/m^3 (mean in ultrafine particles ≤0.2 µm)	Mortality from ischemic heart disease	↑
Peralta et al. 2021 Cohort study; 563 male participants of the Veterans Administration Normative Aging Study in Massachusetts (mean age 74.1 years); exposure modeled for each subject's residence between 2000 and 2011 (United States).	Modeled concentration in ambient air: 3.7 ng Cu/m^3 (mean in $PM_{2.5}$)	Heart-rate corrected QT interval	↓ (improved) with 4-day moving average copper concentration
Liu and Liang 2023 Cross-sectional, 10,175 adult participants >40 years old (~48% male, mean age 57 years) in NHANES (2013–2014) (United States)	Estimated dietary intake based on 24-hour recall: 1.24 mg Cu/day (mean)	Severity of abdominal aortic calcification	↓
Yin et al. 2021 Cross-sectional, 39,757 adult participants (~49% male, mean age 49.6 years) in NHANES (2005–2018) (United States)	Estimated dietary intake: 1.1 mg Cu/day (median)	Prevalence of cardiovascular diseases	↓
Yang et al. 2022 Cross-sectional, 10,550 adult participants (~48% male, mean age 50 years) in NHANES (2013–2018) (United States)	Estimated dietary intake based on 24-hour recall: Q1: <0.799 mg Cu/day Q2: ≥0.799 to <1.072 Q3: ≥1.072 to <1.42 Q4: ≥1.42	Risk of stroke	↓
Tong et al. 2022 Case-control, 80 hypertensive children and 84 age- and sex-matched controls (6–12 years of age) (China)	Estimated dietary intake based on questionnaire: 1.56 mg Cu/day (cases) 2.09 mg Cu/day (controls)	Hypertension	↓

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Copper and Cardiovascular Effects

Reference, study type, and population	Exposure	Outcome evaluated	Result
He et al. 2022 Prospective cohort, 12,245 participants in China Health and Nutrition Survey, followed for mean 6.1 years (China)	Estimated dietary intake based on 24-hour recall at baseline: ≥1.57 mg Cu/day	Incident hypertension	↑
	<1.57 mg Cu/day	Incident hypertension	↓

↑ = association; ↓ = inverse association; NHANES = National Health and Nutrition Examination Survey; $PM_{2.5}$ = particulate matter ≤2.5 μm; Q = quartile

Epidemiological studies of dietary copper intake have also evaluated cardiovascular effects (Table 2-7). Inverse associations between estimated dietary intake of copper and cardiovascular effects (including severity of abdominal aortic calcification, prevalence of cardiovascular diseases, or risk of stroke) were observed in three cross-sectional studies of adult participants in NHANES surveys (Liu and Liang 2023; Yang et al. 2022; Yin et al. 2021). A small case-control study in China reported an inverse association between estimated dietary copper intake and childhood hypertension (Tong et al. 2022). In a larger prospective cohort study in China, He et al. (2022) observed a U-shaped dose-response relationship between estimated dietary copper intake and incident hypertension. The incidence of hypertension decreased with intake estimates up to 1.57 mg Cu/day, but at higher doses, the incidence of hypertension increased (He et al. 2022).

A number of case studies reported cardiovascular effects following intentional or accidental ingestion of various copper compounds, including copper sulfate, copper oxychloride, and copper-8-hydroxyquinolate. The most common symptoms were elevated pulse rate, low blood pressure, and tachycardia (Cho et al. 2018; Franchitto et al. 2008; Griswold et al. 2017; Gunay et al. 2006; Gupta et al. 2018; Higny et al. 2014; Sinkovic et al. 2008; Sood and Verma 2011). Two case studies reported elevated blood pressure following accidental ingestion of copper sulfate: one in a 65-year-old man who accidentally ingested approximately 10 g copper sulfate diluted in water and one in a 22-year-old man who accidentally ingested 1 cup of copper sulfate powder (Hassan et al. 2010; Higny et al. 2014). Ingestion of copper sulfate crystals resulted in fatal cardiac arrest in two cases: one in a 26-year-old man who intentionally ingested an unknown amount of crystals and another in a 60-year-old man who accidentally ingested 15–18 mg of crystals (Gupta et al. 2018; Griswold et al. 2017). A 30-year-old female who intentionally ingested dehydrated copper sulfate developed swollen feet in addition to low

blood pressure (Yadla et al. 2015). Thinned arteries, congested veins, and cardiac failure were reported in a 19-year-old woman who intentionally ingested an unknown amount of a liquid fungicide whose sole active ingredient was 50% copper oxychloride (Gunay et al. 2006).

No studies were located regarding cardiovascular effects in humans following dermal exposure to copper, but exposure by routes other than those described previously has led to cardiovascular changes. A 40-year-old woman developed toxic myocarditis followed by a 2-minute-long cardiac arrest after intentionally inserting an unknown amount of copper sulfate into her rectum (Moussiegt et al. 2020). A 29-year-old pregnant woman developed peripheral vasoconstriction after intentionally vaginally inserting an unknown amount of copper sulfate powder diluted in water (Motlhatlhedi et al. 2014). A 22-year-old man who was found dead had developed subpleural and sub-epicardial hemorrhage after intentionally injecting approximately 1 g copper sulfate into his arm (Behera et al. 2007). A 41-year-old woman developed low blood pressure and rapid atrial fibrillation after intentionally injecting 2.5 g copper glycinate subcutaneously into her arm at three sites (Oon et al. 2006).

No toxicity studies were located regarding cardiovascular effects in animals following inhalation exposure to copper. A 7-day gavage exposure to 39.8 mg Cu/kg/day as copper sulfate resulted in a significant increase in serum cardiac troponin I as well as apparent histopathological changes (blood vessel congestion, inflammatory cell infiltration, degenerative changes) in the hearts of rats (Sarawi et al. 2021). However, the study authors did not report the incidence or severity of the histopathological changes, so effect levels could not be determined.

Well-conducted intermediate-duration oral studies have not shown effects on heart histology in rats exposed to copper monochloride by gavage for 4–5 weeks (Chung et al. 2009) or in rats or mice exposed to copper sulfate pentahydrate in drinking water for 15 days or in feed for 15 days or 13 weeks (NTP 1993).

In male Wistar rats exposed to 50.9 mg Cu/kg/day of copper sulfate for 30 days, flabby, enlarged, congested hearts were seen at gross necropsy; histopathology was not examined (Khushboo et al. 2018). Based on marked decreases in reported water and food intake (40 and 30% less than controls, respectively) (Khushboo et al. 2018), it is likely that these animals were dehydrated and malnourished. Increased blood pressure was reported in two intermediate-duration studies of male Wistar rats (Arafa et al. 2019; Liu and Medeiros 1986). Exposure to 14 mg Cu/kg/day as copper carbonate in feed for 15 weeks resulted in ~20% higher systolic blood pressure (Liu and Medeiros 1986), while exposure to

50.9 mg Cu/kg/day as copper sulfate pentahydrate (via gavage) for 90 days resulted in 33% higher systolic blood pressure (Arafa et al. 2019).

2.6 GASTROINTESTINAL

There are few human studies documenting gastrointestinal effects after inhalation exposure to copper, and no human studies of these effects after dermal exposure to copper were located. In workers involved in grinding and sieving copper dust, anorexia, nausea, and occasional diarrhea were reported; more rarely, vomiting was also observed (Suciu et al. 1981). Exposure levels declined over time, from 464 to 111 mg Cu/m^3 over a 3-year period, and gastrointestinal symptom frequency declined over the same time period. While initial exposure was primarily via the inhalation route, it is possible that the gastrointestinal effects were due to oral exposure to copper. Ingestion may have resulted from mucociliary clearance of copper particles deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract. One case study reported vomiting in a 2-year-old female child following accidental inhalation of a copper powder (Donoso et al. 2007).

Gastrointestinal effects of copper in humans exposed orally have been documented in controlled exposure studies, community health investigations of copper in drinking water, and epidemiological studies. Controlled human exposure studies are included in the LSE table (Table 2-2) and discussed in detail below. Epidemiological studies that met inclusion criteria (see Appendix C, Section C.2.2), community health investigations, and case reports/case series are described in text below.

Controlled Human Oral Exposure Studies. Controlled human exposure studies of gastrointestinal effects primarily used drinking water administration. The doses calculated from these studies represent the exposure from copper in drinking water only; several studies did survey participants on their diets, but copper intake from normal diets was not considered in the dose estimations.

Several experiments designed to identify the threshold for gastrointestinal effects were performed, typically involving adults ingesting a single dose of copper sulfate following an overnight fast (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001). The lowest exposure level resulting in gastrointestinal effects was identified by Olivares et al. (2001), who observed an increased incidence of nausea at 0.012 mg Cu/kg (4 mg Cu/L). No nausea was reported by subjects exposed to lower doses in this study (Olivares et al. 2001). At 0.018 mg Cu/kg (6 mg Cu/L), a significant increase in the incidence

of vomiting was also observed. Administering the copper sulfate in an orange-flavored drink increased the threshold for nausea to 8 ppm (0.022 mg Cu/kg) (Olivares et al. 2001).

Two multinational studies by Araya et al. (2001, 2003c) reported a threshold of 6 mg Cu/L for increased incidence of nausea. In a study by Araya et al. (2001), no nausea was reported following exposure at doses of ≤0.012 mg Cu/kg (4 mg Cu/L), while nausea occurred in 17/179 adults exposed to 0.018 mg Cu/kg (6 mg Cu/L). In this study, females appeared more sensitive to developing nausea following copper ingestion. In Araya et al. (2003c), a single exposure to 0.09 mg Cu/kg (6 mg Cu/L) resulted in nausea in 50/269 females, while no nausea occurred at 0.06 mg Cu/kg. This study determined that both the copper concentration and the total copper dose are important variables in predicting a gastric response; as the concentration and dose increase, the probability of eliciting nausea increases (Araya et al. 2003c).

Nausea and vomiting effects were confirmed in two studies each testing a single exposure to 10 mg Cu/L as copper sulfate in water: 9/30 adults reported nausea in one study (Araya et al. 2003a) and 6/31 adults reported nausea while 2/31 reported vomiting in the other (Gotteland et al. 2001). These studies also examined physiological alteration in the intestines (Araya et al. 2003a; Gotteland et al. 2001). Gotteland et al. (2001) found significant increases in gastric permeability to sucrose following the bolus ingestion of 10 ppm copper as copper sulfate (0.03 mg Cu/kg); no alterations in intestinal permeability to lactulose/mannitol were found. The increased gastric permeability was independent of gastrointestinal symptoms. A significant delay in decreasing the stomach's antral area was found during the first hour after bolus ingestion of 10 ppm copper as copper sulfate (0.046 mg Cu/kg) (Araya et al. 2003a). This change in antral area is suggestive of a delay in gastric emptying. As with gastric permeability, this effect was independent of gastrointestinal symptoms.

Repeated exposure studies conducted in adults exposed to copper in drinking water have confirmed the threshold for gastrointestinal symptoms (Araya et al. 2003b, 2004; Olivares et al. 2001; Pizarro et al. 1999, 2001). Abdominal pain, nausea, and/or vomiting were observed in women drinking water containing 5 mg Cu/L (0.096 mg Cu/kg) copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). The occurrence of gastrointestinal effects was not significantly different between subjects ingesting 10 mg Cu/L as copper sulfate or copper oxide (Pizarro et al. 2001).

A study by Pizarro et al. (1999) demonstrated a dose-response relationship between copper sulfate exposure and gastrointestinal symptoms (nausea, vomiting, and abdominal pain) in healthy adult women.

Each study participant consumed either 0, 1, 3, or 5 mg Cu/L of copper as copper sulfate in their drinking water daily for 2 weeks with a 1-week rest period before starting a new exposure. Based on measured water concentrations and water intake, the study authors reported doses of 0.04 (control), 1.74, 4.68, and 7.94 mg Cu from water[2], corresponding to doses of 0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day, respectively. The incidences of abdominal pain, nausea, diarrhea, and/or vomiting were reported, and no dose-response relationship for copper exposure and diarrhea was found (Pizarro et al. 1999). Abdominal pain, nausea, and vomiting were dose-related, and incidences for these symptoms were significantly higher in groups that consumed ≥0.0731 mg Cu/kg/day (≥3 mg Cu/L) than in groups consuming ≤0.0272 mg Cu/kg/day (≤1 mg Cu/L) (Pizarro et al. 1999).

In a 2-month study by Araya et al. (2003b, 2004), 65/355 male and female adults exposed to 0.106 mg Cu/kg/day as copper sulfate (4 mg Cu/L in water used for drinking and food preparation) reported at least one gastrointestinal symptom, among nausea, vomiting, diarrhea, and abdominal pain, at some point during the exposure period. The incidence of symptoms was significantly higher for this dose group compared to subjects exposed to 0.055 mg Cu/kg/day (2 mg Cu/L) (Araya et al. 2003b, 2004). These investigators showed that the incidence of gastrointestinal symptoms increased with copper exposure (concentration in water and volume of water ingested) and females appeared to be at a higher risk for symptoms than males. As the duration of exposure increased, the concentration in water necessary to achieve a positive gastrointestinal response increased (Araya et al. 2003b, 2004).

Abdominal pain and diarrhea were also reported in several of the controlled exposure studies (Araya et al. 2003b, 2004; Pizarro et al. 1999, 2001), but these symptoms did not show a clear relationship to dose among adults. A study of 56 healthy babies who received 2 mg Cu/L of copper sulfate in water daily for 9 months did not observe any significant difference in the incidence of gastrointestinal effects (Olivares et al. 1998). Two babies who were formula-fed had diarrhea, but this was not likely to be exposure-related, as none of the breastfed babies had symptoms. Controls were exposed to copper doses ranging between 0.123 and 0.174 mg Cu/kg/day and experimental infants were exposed to doses ranging from 0.0522 to 0.319 mg Cu/kg/day (Olivares et al. 1998).

Epidemiological Investigations. Two cohort studies that met inclusion criteria examined the association between occurrence of gastrointestinal symptoms and exposure to copper in drinking water. Buchanan et

[2]Pizarro et al. (1999) estimated that the subjects' copper intake from diet ranged between 1.5 and 1.9 mg Cu/day (corresponding to doses of 0.023–0.29 mg Cu/kg/day) over the study; these amounts were not added to the doses received from water.

al. (1999) observed no increased risk of gastrointestinal symptoms during the prior 2 weeks when comparing individuals in homes with drinking water copper concentrations >3 mg Cu/L and those with drinking water copper concentrations <1.3 mg Cu/L (Buchanan et al. 1999). Similarly, Pettersson et al. (2003) observed no association between risk of diarrhea or vomiting among children and copper concentrations in water. These study authors evaluated children's exposure both by intake (<0.5, 0.05–1.0, or >1.0 mg Cu/day) and by concentration (≤2 or >2 mg Cu/L); neither analysis showed a relationship to diarrhea nor to vomiting (Pettersson et al. 2003).

Case Reports/Case Series and Community Health Investigations. Gastrointestinal effects have been documented in case reports of humans after intentional or accidental ingestion of copper substances, and in health investigations of communities with elevated copper levels in drinking water. The most common effects include abdominal pain, nausea, vomiting, diarrhea, and melena (black stool), which typically occur shortly after ingestion and are not persistent (Gupta et al. 2023; Knobeloch et al. 1994, 1998; Shankar et al. 2023; Tsao et al. 2020).

A 1-year-old infant girl developed vomiting and diarrhea within 20 minutes of consuming cake frosting that had been mixed with a non-edible colored dust containing copper. Analysis of the frosting showed a content of 21 mg Cu/g frosting (Tsao et al. 2020). The child's symptoms resolved within a day and she had no long-term effects (Tsao et al. 2020). Gastrointestinal ulcerations and hemorrhaging were observed following copper sulfate ingestion in several case studies (Banerjee et al. 2023; Du and Mou 2019; Franchitto et al. 2008; Galust et al. 2023; Gamakaranage et al. 2011; Griswold et al. 2017; Lubica et al. 2017; Malik and Mansur 2011; Shankar et al. 2023). There have been several reports of upper gastrointestinal effects, including oral mucositis, pharyngeal or esophageal edema and/or corrosive injury, and odynophagia, following copper sulfate ingestion (Galust et al. 2023; Higny et al. 2014; Hassan et al. 2010; Shankar et al. 2023). Dysphagia was reported in a 66-year-old man whose neighbor frequently treated his orchard with copper sulfate, resulting in a "blue dust cloud" to which the man was exposed (Perestrelo et al. 2021). The nature of the patient's exposure was not clearly defined in the report, but may have included both inhalation and oral routes (Perestrelo et al. 2021). Inflammation of the gallbladder was observed in two cases: one in a 19-year-old woman who intentionally ingested an unknown amount of pesticide containing copper oxychloride and another in a 40-year-old man who intentionally ingested 50 mL of a solution containing 33.5% weight by volume copper-8-hydroxyquinolate (Gunay et al. 2006; Yang et al. 2004).

The Wisconsin Division of Health conducted several community health investigations of copper in drinking water (Knobeloch et al. 1994, 1998). Some were in response to community complaints about gastrointestinal symptoms or bitter-tasting water and others were in response to reports of elevated copper concentrations. During the investigations, residents were asked to complete questionnaires about general health and gastrointestinal symptoms. These community health investigations suggested an association between copper intake from drinking water and gastrointestinal symptoms, but the analyses are not sufficiently rigorous to provide independent evidence; copper concentration data generally reflected convenience samples; participant recruitment (e.g., via public meetings to discuss copper levels) may have led to selection bias; covariates/alternative causes for the symptoms were not considered; and the numbers of participants in the investigations were typically quite small.

Animal Studies. No studies were located regarding gastrointestinal effects in animals following inhalation exposure to copper. Gastrointestinal effects have been reported in multiple animal studies of oral administration. In rats administered a single high dose of 50.9 mg Cu/kg/day as copper sulfate pentahydrate, gross necropsy findings included thickened stomach wall with corrugated mucosa (Khushboo et al. 2018). All four shrews exposed to 31 mg Cu/kg as copper sulfate pentahydrate by gavage experienced emesis (vomiting), while exposure to 2.5 mg Cu/kg did not induce vomiting in shrews (Yamamoto et al. 2004). In the same study, rats, which do not possess an emetic reflex, responded to exposure by consuming more kaolin, a common response of rats to emetic agents (Yamamoto et al. 2004).

A single dose of copper chloride (14 mg Cu/kg) administered to rats resulted in duodenal histopathological changes including loss of enterocyte arrangement and brush border, necrotic debris, and lymphocyte and plasma cell accumulations (Husain et al. 2021). Focal intestinal ulceration was reported in mice exposed to 4 mg Cu/kg/day as copper sulfate for 7 days, with no effects at 2 mg Cu/kg/day (Kadammattil et al. 2018); however, the incidence and severity of the lesions was not reported.

Intermediate-duration animal studies have demonstrated tissue damage in the stomach after oral exposure to copper compounds. Increased incidences of squamous cell hyperplasia in the stomach was observed in male and female rats exposed to 13 and 3 mg Cu/kg/day (respectively) as copper monochloride by daily gavage in a combined repeat-dose and reproductive/developmental toxicity screening study (Chung et al. 2009). Hyperplasia with hyperkeratosis of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach was observed in male and female rats exposed to 44–46 mg Cu/kg/day for 15 days or 33–34 mg Cu/kg/day for 13 weeks in their diet as copper sulfate, and in mice

exposed to 197–216 mg Cu/kg/day for 15 days or 187–267 mg Cu/kg/day for 13 weeks in their diet as copper sulfate (NTP 1993). No effects were seen at lower doses of copper in the diet of rats or mice. Animals exposed to copper sulfate in drinking water for 15 days did not show any gastrointestinal effects, including rats exposed to doses up to 26–29 mg Cu/kg/day and mice exposed to doses up to 24–36 mg Cu/kg/day (higher doses were lethal to many of the animals) (NTP 1993).

EPA (2006) reviewed an unpublished developmental toxicity study in rabbits in which four of 21 rabbits exposed to 18 mg Cu/kg/day (as copper hydroxide administered via gavage on GDs 7–28) exhibited stomach hemorrhage, ulceration, or both; deaths were also observed at this dose (reviewed by EPA 2006). As reported in EPA (2021a), *Registration review draft risk assessment for copper 8-quinolinolate (bis(8-quinolinolato)copper(II))*, an unpublished study submitted to EPA reported that dogs exposed to ≥50 mg/kg/day copper 8-quinolinolate by daily capsule for 90 days exhibited vomiting as well as reddened mucosa and hyperemia in the gastrointestinal tract. EPA (2021a) also reviewed an unpublished study of rats exposed by diet for 90 days in which hypertrophy of the duodenal villi was observed in males at doses ≥100 mg/kg/day copper 8-quinolinolate. Based on another study submitted to the Agency, EPA (2021a) reported that male mice exposed to 207.7 mg/kg/day copper 8-quinolinolate in an 80-week carcinogenicity study exhibited increased incidences of stomach ulcers.

Mechanisms. Studies in monkeys, dogs, shrews, and ferrets provide 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 shrews, abdominal vagotomy prevented emesis at low doses of copper sulfate but not at higher doses (Horn et al. 2014). In monkeys, administration of compounds that block 5-HT_3 receptors also resulted in a decrease in emesis following oral or intravenous administration of copper sulfate (Fukui et al. 1993). In contrast, 5-HT_3 blockers did not affect the occurrence of emesis in dogs (Fukui et al. 1994) or ferrets (Bhandari and Andrews 1991) receiving an oral dose of copper sulfate, but compounds that block 5-HT_4 receptors did inhibit copper-induced vomiting. Fukui et al. (1994) suggested that copper sulfate caused gastrointestinal irritation that resulted in the release of 5-HT and evoked emesis by activation of abdominal visceral afferents through 5-HT_4 receptors.

2.7 HEMATOLOGICAL

Decreased hemoglobin and erythrocyte levels were observed in workers exposed to airborne copper dust levels of 0.64–1.05 mg Cu/m^3 (Finelli et al. 1981); however, it is unknown if copper is causally related to the effects, given that results of hair analysis revealed that the workers had also been exposed to iron, lead, and cadmium, and the study authors did not control for co-exposures (Finelli et al. 1981).

In a controlled exposure study in which 60 adult females were exposed to copper in drinking water daily for 2 weeks, no changes in hemoglobin were seen with doses as high as 0.1 mg Cu/kg/day (Pizarro et al. 1999). Likewise, when seven adult subjects were exposed to copper gluconate daily in capsule form for 12 weeks, there were no changes in hematocrit or mean corpuscular volume compared to pre-exposure values (Pratt et al. 1985).

Numerous case studies have reported hematological effects in humans following intentional or accidental ingestion of copper-containing substances. The most common effects are hemolytic anemia, hemoglobinemia, methemoglobinemia, leukocytosis, and reduced reticulocyte count (Banerjee et al. 2023; Cho et al. 2018; Du and Mou 2019; Franchitto et al. 2008; Gamakaranage et al. 2011; Griswold et al. 2017; Gunay et al. 2006; Gupta et al. 2018, 2023; Lubica et al. 2017; Malik and Mansur 2011; Mortazavi and Jafari-Javid 2009; Perestrelo et al. 2021; Shankar et al. 2023; Sinkovic et al. 2008; Sood and Verma 2011; Valsami et al. 2012; Yadla et al. 2015; Yang et al. 2004). Cyanosis, a blueish discoloration of the skin usually associated with methemoglobin accumulation, has also been reported in several case studies (Banerjee et al. 2023; Du and Mou 2019; Hassan et al. 2010; Malik and Mansur 2011; Sinkovic et al. 2008; Yang et al. 2004).

Hypoxemia and hemolytic anemia were observed in a 2-year-old female child who spilled a copper powder on her face and inhaled some of the powder (Donoso et al. 2007). Methemoglobinemia, leukocytosis, and hemolysis were observed in a 53-year-old man following dermal contact with a hot copper sulfate solution (Park et al. 2018). In a child who had been severely burned, copper sulfate crystals were applied to the burn area, which resulted in hemolytic anemia and increased serum and urine copper levels (Holtzman et al. 1966). Intravascular hemolysis was observed in a 22-year-old man who intentionally injected approximately 1 g copper sulfate solution intravenously (Behera et al. 2007). Hemolytic anemia was observed in a 41-year-old female who intentionally subcutaneously injected a total of 2.5 g copper glycinate in solution via syringe among three different sites on the forearm (Oon et al. 2006). Methemoglobinemia, elevated blood glucose, and increased white blood cell counts were

observed in a 29-year-old woman who intentionally vaginally inserted copper sulfate powder diluted in water in order to terminate an unwanted pregnancy (Motlhatlhedi et al. 2014).

Only one study of hematological effects in animals exposed to copper by inhalation was located. Poland et al. (2022) observed a significant increase in circulating neutrophils in rats exposed to dicopper oxide particles by inhalation for 4 weeks. Neutrophil counts in the blood were significantly increased in males (≥93% compared to control) at 0.35 and 0.7 mg Cu/m^3, and were increased (88%), but not statistically significant, at the highest concentration of 1.76 mg Cu/m^3. In females, circulating neutrophils were significantly increased (118 and 120%) at 0.7 and 1.76 mg Cu/m^3, respectively, compared to control. No other hematology changes were observed.

Several studies examined the hematological effects of copper in rats, mice, pigs, and rabbits following intermediate-duration oral exposures. Evidence for effects on hematological parameters comes primarily from studies of rats, as studies in other species are more limited. In rats exposed for intermediate durations (20–90 days) to doses of 25.5–39.8 mg Cu/kg/day as copper sulfate, decreased hemoglobin concentration, red blood cell counts, and/or hematocrit were observed (Adele et al. 2023; Kumar and Sharma 1987; Kumar et al. 2015; Rana and Kumar 1980). At the high end of the dose range (39.8 mg Cu/kg/day), marked decreases in erythrocyte count (48–52% less than controls) and hemoglobin (38–47% less than controls) were observed (Kumar and Sharma 1987; Rana and Kumar 1980); changes of this magnitude could affect oxygenation. Adele et al. (2023) also observed a decrease in the myeloid:erythroid ratio in the bone marrow of female rats given 39.8 mg Cu/kg/day for 5 weeks. NTP (1993) did not evaluate hematology in its 15-day drinking water and feed studies of rats; however, histopathology evaluation revealed depletion of hematopoietic cells in bone marrow of male and female rats exposed to 196–198 mg Cu/kg/day as copper sulfate in feed. Hematology evaluations in the 13-week feed studies of copper sulfate showed decreases in hematocrit, hemoglobin concentration, mean cell hemoglobin, and/or mean cell volume, along with increased reticulocyte counts in both male and female rats exposed to ≥66–68 mg Cu/kg/day (NTP 1993). Platelet levels were increased in both sexes at the same doses; NTP (1993) suggested that these changes were consistent with reactive thrombocytosis (NTP 1993). Rats exposed to copper chloride by gavage in a combination repeat-dose and reproductive/developmental screening study for 30–38 days exhibited hematology changes (Chung et al. 2009). At the highest dose of 51 mg Cu/kg/day, males showed significant decreases in erythrocyte counts, hemoglobin concentration, mean cell hemoglobin, hematocrit, and mean cell volume, as well as increased platelets, white blood counts, and percentage of neutrophils. Females showed nonsignificant decreases in many of

the same parameters, along with a significant decrease in mean cell hemoglobin and a significant increase in platelet count.

NTP (1993) did not evaluate hematology in mice in the 15-day or 13-week studies. In these studies, there were no histopathology findings related to hematopoiesis in mice. Kvietkauskaite et al. (2004) reported that no hematological effects were observed in mice exposed to copper sulfate doses of 42 mg Cu/kg/day for 19 weeks, but the study authors did not specify the hematological parameters that were analyzed, and data were not shown.

In pigs, significantly decreased hemoglobin levels and increased erythrocyte counts were seen with 16.5–18.7 mg Cu/kg/day as copper carbonate for 46–49 days of exposure (Suttle and Mills 1966). Kline et al. (1971) saw no changes in hemoglobin levels in pigs following 88 days of exposure to 2.7 mg Cu/kg/day as copper sulfate.

Chronic-duration exposure studies in young monkeys found no hematological effects after exposure to a daily dose of 5.5 mg Cu/kg/day as copper gluconate for 3 years; however, lower hemoglobin levels were observed in adults receiving a dose of 7.5 mg Cu/kg/day when compared to the controls (Araya et al. 2012).

2.8 MUSCULOSKELETAL

There are very limited data on musculoskeletal effects of copper and copper compounds in humans or animals, and the only data are for oral exposures. Rhabdomyolysis (breakdown of skeletal muscle) was reported in two case reports, one in a 25-year-old man who intentionally ingested an unknown amount of a substance thought to contain copper and another in a 53-year-old man who intentionally ingested 120 g of copper sulfate (Lubica et al. 2017; Valsami et al. 2012).

Depressed skeletal growth, as measured by tail length, was observed in rats administered 39.8 mg Cu/kg/day as copper sulfate via gavage for 20 days (Rana and Kumar 1980). Rabbits fed 4.83 mg Cu/kg/day as copper sulfate pentahydrate for 5 weeks showed 4–9% increases in the weights of the foreleg and hindlegs, but the effects were not dose related and no further evaluations were performed (Li et al. 2021). Based on radiographic findings, 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).

2.9 HEPATIC

Several disorders of copper homeostasis in humans result in hepatic effects. Wilson's disease, Indian childhood cirrhosis (ICC), and idiopathic copper toxicosis (ICT) are diseases largely defined by accumulation of copper in the liver. These disorders are described briefly below, followed by studies of human and animal exposure to exogenous copper.

Hepatic Effects in Human Disorders of Copper Homeostasis. Wilson's disease is a rare, autosomal, recessive genetic disorder with a prevalence of approximately 30–50 cases per million in most parts of the world, with a gene frequency of 0.56% and carrier frequency of 1 in 90 (Rodriguez-Castro et al. 2015). In Western countries, the gene frequency is generally lower at 0.36% (Liu et al. 2017). It is primarily characterized by low levels of serum ceruloplasmin and by elevated urinary copper excretion, elevated copper levels in the liver, elevated serum free copper, or the presence of Kayser-Fleischer rings (excess copper deposits in the cornea) (Rodriguez-Castro et al. 2015). The accumulation of copper in the liver is due to a genetic mutation in the ATP7B region on chromosome 13q14, resulting in impaired biliary excretion of copper (Liu et al. 2017). Clinical manifestation of the disease varies but is predominantly hepatic or neurological. Liver effects can range from asymptomatic to liver failure and cirrhosis (Rodriguez-Castro et al. 2015), and three types of liver damage are seen: cirrhosis, chronic active hepatitis, and fulminant hepatic failure. In infants with Wilson's disease, the disease is first characterized by excess hepatic copper despite no histologic indications. Symptoms appear with age and include degenerative change in hepatocytes, fibrosis, and cirrhosis (Scheinberg and Sternlieb 1996). The manifestations of Wilson's disease are not considered to be related to exposure to high levels of copper, but rather the individual's impaired excretion of copper. Individuals with Wilson's disease have elevated levels of hepatic copper when consuming diets with average copper intakes (Scheinberg and Sternlieb 1996).

ICC is a type of liver cirrhosis that was previously considered endemic to India but has since been documented in children of non-Indian origin in multiple countries. It is typically seen in infants and young children 6 months to 3 years in age but has also been diagnosed in children up to 11 years of age (Nayak and Chitale 2013). Predisposition to ICC is suspected to be inherited due to its random occurrence among siblings (up to 22% of siblings affected) and mortality due to liver disease in second-degree relatives of affected children (Nayak and Chitale 2013; Pandit and Bhave 1996). Two widely recognized distinctive features of ICC are coarse, dark brown orcein hepatic staining (representing

copper) and intralobular pericellular fibrosis (Pandit and Bhave 1996). Liver copper levels ranging from 790 to 6,654 μg/g dry weight (mean of 939 μg/g) were 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). Interpretation of these study results is limited by the small number of controls and the lack of detail on the control group.

No specific genetic susceptibilities have been linked to ICC, and evidence is inconclusive on whether ICC is caused by external exposure to copper or endogenously through dysregulation of copper in the body (Nayak and Chitale 2013). Several studies suggest that copper overload and liver injury in ICC-diagnosed children resulted from the use of brass vessels for milk storage (Bhave et al. 1987; Tanner 1998; Tanner et al. 1983). Other studies conversely conclude that excess dietary copper was not a likely cause of copper overload in ICC-diagnosed children, including in a 2006 multi-center study in India that compared 227 cases of confirmed ICC with 426 controls (Nayak and Chitale 2013; Sethi et al. 1993). This conclusion is supported by several epidemiological studies of high copper-exposed populations that failed to reveal liver injury in children (Nayak and Chitale 2013).

ICT is believed to be caused by an autosomal-recessive genetic defect in copper metabolism combined with excess dietary copper (Müller et al. 1998; Nayak and Chitale 2013). In the literature, ICT is also referred to as ICC-like liver disease, primary copper toxicosis, and Tyrolean infantile cirrhosis. In general, a few rare, sporadic cases of ICC-like diseases have been reported in 11 countries other than India (Nayak and Chitale 2013). 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 for one to four children or at least one adult (Harada et al. 2020; Nayak and Chitale 2013). Compiling the data from these studies, Müller et al. (1998) found a number of consistent patterns: (1) the age of onset of clinical symptoms occurring 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 (ALP), bilirubin, albumin, and prothrombin time; and (5) marked panlobular and pericellular fibrosis associated with a usually mild inflammatory infiltrate, ballooning degeneration of hepatocytes, and an abundance of Mallory bodies. Previously, ICT was attributed to excess intake of exogenous forms of copper but is more likely attributable to a genetic defect along with abnormal copper metabolism (Harada et al. 2020; Nayak and Chitale 2013). A genealogic investigation conducted by Müller et al. (1996) provided suggestive evidence that the disease is transmitted in an autosomal recessive mode.

Hepatic Effects of Human Exposure to Exogenous Copper. Hepatomegaly was observed in workers involved in grinding and sieving copper dust (Suciu et al. 1981). The exposure levels declined over time, from 464 to 111 mg Cu/m^3 over a 3-year period; however, the prevalence of hepatomegaly increased, rather than decreased, during this time period. One case study reported elevated AST and bilirubin in a 2-year-old female who accidentally inhaled a copper powder (Donoso et al. 2007).

Hepatic clinical chemistry parameters (serum ALT, AST, γ-glutamyl transferase [GGT], and/or LDH) were evaluated in several controlled human oral exposure studies. No significant changes in serum enzyme activities were seen at doses up to 0.138 mg Cu/kg/day as copper sulfate in drinking water for up to 2 months (Araya et al. 2003b; Pizarro et al. 1999, 2001), in the diet for 6 weeks (O'Connor et al. 2003), or in capsule form for 6 months (Rojas-Sobarzo et al. 2013). Similarly, in a study of seven adults receiving capsules (orally) containing 0.15 mg Cu/kg/day as copper gluconate for 12 weeks, no significant alterations in serum enzyme activities were found (Pratt et al. 1985). No alterations in total bilirubin levels or serum ALT, AST, or GGT activities were found in a study of infants (3 months of age at study initiation) exposed to 0.319 mg Cu/kg/day as copper sulfate in drinking water for 9 months (Olivares et al. 1998).

Numerous case reports documented hepatic effects in humans following accidental or intentional ingestion of copper substances, including copper sulfate, copper oxychloride, and copper-8-hydroxyquinolate. The most common effects were altered liver enzyme activity, including changes in serum AST, ALT, ALP, and LDH (Du and Mou 2019; Griswold et al. 2017; Gunay et al. 2006; Hassan et al. 2010; Malik and Mansur 2011; Mortazavi and Jafari-Javid 2009; Sinkovic et al. 2008; Shankar et al. 2023; Yadla et al. 2015; Yang et al. 2004). Liver impairment was reported in two cases that provided limited details: one in a 26-year-old man who intentionally ingested approximately 30 g copper sulfate and another in a 53-year-old woman who intentionally ingested 120 g copper sulfate (Gamakaranage et al. 2011; Lubica et al. 2017). A 17-year-old boy who ingested 10 g cupric sulfate developed hemolytic jaundice and a 19-year-old woman who ingested an unknown amount of a copper oxychloride-containing pesticide developed jaundice of the conjunctivae (Du and Mou 2019; Gunay et al. 2006). 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 levels and AST activity, and elevated bile salts in the urine were found in five of the individuals with jaundice. In case reports of lethal ingestion of copper sulfate, jaundice (Akintonwa et al. 1989), centrilobular congestion (Lamont and Duflou 1988), and acute hepatotoxicity (Ahasan et al. 1994) have

been reported. O'Donohue et al. (1993) reported a case of an adult with jaundice and hepatomegaly following 3 years of exposure to copper in supplements. For 2 years, the individual had ingested 30 mg Cu/day followed by 1 year of 60 mg Cu/day. Among six patients examined for chronic copper poisoning, five patients suffered from hepatopathy (Eife et al. 1999). Copper concentrations in tap water of the examined patients ranged from 0.1 to 16.9 mg Cu/L (Eife et al. 1999). Two studies of infants up to 12 months of age who were exposed to ≥0.8 mg Cu/L in household water did not find significant alterations in serum parameters of liver function (serum AST, ALT, or GGT) or alterations in liver ultrasound imaging (Zietz et al. 2003a, 2003b).

Data regarding hepatic effects in humans following dermal exposure to copper are limited to one case study. Elevated serum AST and bilirubin and reduced serum albumin and total protein were observed in a 53-year-old man who slipped and landed on a hot copper sulfate solution on the floor of his workplace, resulting in burns primarily to his legs (Park et al. 2018). It is unclear whether the liver effects were attributable to copper exposure or physical burns, which often result in cholestasis.

Hepatic effects were observed in humans following intentional injection of copper substances. A 22-year-old man intravenously injected approximately 1 g copper sulfate mixed with water into his arms and developed substantial hepatic necrosis (Behera et al. 2007). A 41-year-old woman subcutaneously injected 2.5 g copper glycinate and then developed acute hepatic failure with elevated AST and reduced ALT (Oon et al. 2006). Elevated AST and ALT were observed in a 29-year-old pregnant woman who intentionally vaginally inserted an unknown amount of copper sulfate powder dissolved in water (Motlhatlhedi et al. 2014).

Animal Studies. No treatment-related changes in liver weight or liver histopathology were observed in rats exposed to dicopper oxide or copper sulfate pentahydrate by whole-body inhalation at concentrations up to 8.9 mg Cu/m^3 for 2 weeks or to dicopper oxide concentrations up to 1.76 mg Cu/m^3 for 4 weeks (Poland et al. 2022). No other studies of liver effects in animals exposed by inhalation were located.

The hepatotoxicity of copper in animals is described and investigated in numerous acute- and intermediate-duration oral exposure studies. Many of these studies were designed to evaluate the protective effects of various antioxidants (e.g., curcumin) against the hepatic effects of copper. These studies typically reported histopathology findings qualitatively using representative photomicrographs, and these often provided too little information to determine effect levels.

Studies of hepatic effects in acute-duration oral studies were limited by lack of histopathology evaluation or failure to report quantitative histopathological findings. In rats exposed to 119 mg Cu/kg/day as copper sulfate for 7 days, serum ALT[3] was increased nearly 3-fold relative to controls (Alhusaini et al. 2018a). No other hepatic endpoints were evaluated. Another study by the same authors reported a similar change in serum ALT at a dose of 39.8 mg Cu/kg/day; in this study, serum LDH was increased >2-fold, and serum AST was also increased relative to controls (Alhusaini et al. 2018b). Results of histopathology examination were reported qualitatively, and consisted of massive cellular degeneration and necrosis (Alhusaini et al. 2018b). Haywood (1980) reported parenchymal cell hypertrophy in the liver, while Haywood and Comverford (1980) reported increased serum ALT activity, in small groups of male rats given 300 mg Cu/kg/day in feed as copper sulfate for 1–2 weeks. Mice exposed to a single gavage dose of copper sulfate at doses between 0.4 and 4 mg Cu/kg/day reportedly exhibited histopathological changes ("lower cellularity and hemorrhage") in the liver; however, the study authors did not provide incidences or severity of the effect in the exposed or control groups, so effect levels could not be determined. (Kadammattil et al. 2018).

Intermediate-duration oral studies reported hepatic effects in various mammal species. Among these, a few studies were designed to evaluate systemic toxicity and dose-response relationships, including the Chung et al. (2009) combined repeat-dose and reproductive/developmental screening study of copper monochloride in rats and the NTP (1993) 15-day and 13-week studies of copper sulfate pentahydrate in rats and mice. These studies evaluated liver weight and histopathology, and in some cases clinical chemistry as well, and reported results quantitatively. Chung et al. (2009) did not observe any changes in clinical chemistry, liver weights, or liver histology in male or female rats exposed by gavage to doses up to 51 mg Cu/kg/day for 30 and 38 days, respectively. In the NTP (1993) 15-day drinking water studies, no hepatic effects were seen after exposure to doses up to 26–29 mg Cu/kg/day (rats) or 24–36 mg Cu/kg/day (mice); higher doses were associated with animal deaths in both species. In the NTP (1993) feed studies, hepatic effects were seen in rats, but not in mice. Male and female rats exposed for 15 days via feed exhibited minimal to mild mononuclear inflammatory cell infiltrate in the liver at doses of 198 mg Cu/kg/day (males) and 285 mg Cu/kg/day (females). In the 13-week feed study, dose-dependent increases in the incidence of chronic active inflammation in the liver were seen in male rats at 33 mg Cu/kg/day and in female rats at 68 mg Cu/kg/day. Chronic active inflammation with focal necrosis was first seen in 1 of 10 male rats at 33 mg Cu/kg/day and in all male rats at 66 mg Cu/kg/day. Males also showed a doubling of serum ALT at 33 mg Cu/kg/day. No hepatic effects were seen in mice exposed via

[3]In the absence of information on other liver endpoints, increases in serum AST or ALT activities at least 2–3-fold higher than controls were considered to be adverse.

diet to doses up to 717–780 mg Cu/kg/day for 15 days or doses up to 815–1,058 mg Cu/kg/day for 13 weeks NTP (1993).

The majority of other studies in rats exposed to copper sulfate by gavage or via diet provide support for the hepatic effect levels identified by the NTP (1993) studies. In these studies, serum chemistry changes (increases in serum ALT and AST) and histopathological changes consisting of inflammation, necrosis, and hepatocyte degeneration were reported at doses ≥40 mg Cu/kg/day for at least 3 weeks (Fuentealba et al. 2000; Kumar and Sharma 1987; Haywood 1980; Haywood and Comerford 1980; Haywood and Loughran 1985; Rana and Kumar 1980; Sakhaee et al. 2012; Seven et al. 2018). A few intermediate-duration studies reported hepatic effects in rats at lower doses of copper (as the sulfate). Kumar et al. (2015, 2016a, 2016b) reported marked (>2-fold) increases in serum ALT, AST, and bilirubin, as well as significant increases in the severity of liver histopathological changes (hepatocellular degeneration and hemorrhage, necrosis, fatty change) after 90 days of exposure to copper sulfate pentahydrate by daily gavage at doses ≥25.5 mg Cu/kg/day. Incidences of the histopathological changes were not reported, but the liver lesions were graded as severe after 90 days (Kumar et al. (2015, 2016a, 2016b). Patwa and Flora (2020) observed increased severity of necrosis of hepatocytes, distorted sinusoidal space, and central vein distortion (scored as moderate to severe, incidences not reported) in the livers of male rats given 8 mg Cu/kg/day by gavage for 16 weeks. In another study designed to evaluate the mitigating effects of a plant-based antioxidant, Temiz et al. (2021) reported liver lesions (dilatation of sinusoids, hepatocellular degeneration, coagulation necrosis, and inflammatory cell infiltration) without biologically significant changes in serum AST, ALT, or LDH in all rats exposed to 3.9 mg Cu/kg/day by gavage twice per week for 4 weeks.

Hashish and Elgaml (2016) reported similar histopathological changes (acute swelling of hepatocytes, hepatocytes with coagulative necrosis, and mild hyperplasia of the bile duct epithelium) in rats exposed to 1.6 mg Cu/kg/day as copper sulfate for 30 consecutive days, but did not provide quantitative information on the effects (incidence or severity), precluding determination of effect levels. Adele et al. (2023) observed no change in relative liver weight in female rats given 39.8 mg Cu/kg/day as copper sulfate for 5 weeks, but did not evaluate any other hepatic endpoints.

A handful of studies have evaluated limited hepatic effects in rats exposed to other copper compounds. Rats exposed to copper acetate in drinking water at a dose of 8.6 mg Cu/kg/day exhibited increased serum AST (>2-fold) after 90 days; no other hepatic endpoints were evaluated (Epstein et al. 1982). Wistar male rats showed a 30% decrease in relative liver weight and enlarged liver with dark spots and swollen

borders, friable and yellow in color, following 50.9 mg Cu/kg/day as copper sulfate for 30 days (Khushboo et al. 2018). Sugawara et al. (1995) observed >2-fold increases in serum ALT and AST in rats exposed to 34 mg Cu/kg/day as copper chloride in the diet for 60 days. When male rats received 60 mg Cu/kg/day as tribasic copper chloride in food for 24 weeks, decreased hepatocyte count and hepatocyte area; damaged, disordered, or absent hepatic cords; and increased numbers of cells with hyperchromatic nuclei and concentrated cytoplasm were observed (Yu et al. 2021a). No changes in the ratio of liver to brain weight or serum AST, ALT, or ALP activity were seen at this dose, but at the high dose of 120 mg Cu/kg/day, serum enzyme levels were increased nearly 2-fold. Abe et al. (2008) found no significant difference in liver weight in Fischer 344 rats receiving 62 mg Cu/kg/day as copper gluconate for 6 weeks compared to controls.

NTP (1993) conducted a 13-week study in rats fed copper sulfate and noted that copper accumulation in the liver of males appeared dose-related, as did chronic active tissue inflammation in both sexes. In females, there were no effects at doses ≤34 mg Cu/kg/day. However, at 68 mg Cu/kg/day, chronic active liver inflammation was reported in 6/10 females, and it was reported in all females at the highest dose of 134 mg Cu/kg/day (NTP 1993). Chronic active inflammation with focal necrosis was first seen in 1 of 10 male rats at 33 mg Cu/kg/day and in all male rats at 66 mg Cu/kg/day. No effects were noted in males exposed to 8–16 mg Cu/kg/day (NTP 1993). In the 15-day studies, males showed no histological changes at 29–92 mg Cu/kg/day as copper sulfate, but there was liver inflammation manifested as minimal to mild mononuclear inflammatory cell infiltrate at 198 mg Cu/kg/day. No histological changes were observed in any females in the 15-day studies, with no effects at doses of 31–285 mg Cu/kg/day as copper sulfate (NTP 1993). The 15-day NTP animal studies tested lower doses in both sexes but did not evaluate serum chemistry changes. Increased incidences of granular and vacuolar degeneration of hepatocytes, necrotic hepatocytes, and disordered hepatic cord arrangement were reported in mice exposed to ≥4 mg Cu/kg/day as copper sulfate for 42 days (Liu et al. 2021c). The same findings were reported without quantitative information by Liu et al. (2020a, 2020b, 2021b) and Wu et al. (2020); these publications were by the same group of investigators and appear to reflect a single experiment. Biologically significant increases in serum AST and/or ALT were reported in mice exposed to 16 mg Cu/kg/day for 20 days (Dab et al. 2023) or 80 mg Cu/kg/day for 42 days (Sakhaee et al. 2014) (as copper sulfate) in studies that did not evaluate other hepatic endpoints.

An unpublished study submitted to EPA and summarized in EPA (2021a), *Registration review draft risk assessment for copper 8-quinolinolate (bis(8-quinolinolato)copper(II))*, reported significant increases in

serum AST, ALT, and bilirubin (males only), as well as increased incidences of diffuse degeneration of the liver, in male and female rats exposed to doses ≥100 mg/kg/day copper 8-quinolinolate.

Studies of liver toxicity in species other than rats and mice are limited. No hepatic effects were observed in pigs given 3.62 mg Cu/kg/day as copper sulfate in feed for 6 weeks (Zhang et al. 2020). Two out of six pigs fed a diet containing 16.5 mg Cu/kg/day as copper carbonate for 46 days displayed jaundice, while five out of six pigs given 18.7 mg Cu/kg/day for 49 days displayed jaundice and AST levels elevated by >100%, compared to controls (Suttle and Mills 1966). No changes were observed in serum liver enzymes or liver histology changes in rhesus monkeys given supplemental copper in formula (6.6 mg Cu/L) from birth to 5 months of age (Araya et al. 2005). The study authors did not provide information on the intake of formula, so dose estimates could not be made for this study, and it is not included in the LSE table or figure.

Data pertaining to hepatic effects in animals exposed chronically were limited to one monkey study. A study of young tufted capuchin monkeys exposed to copper (as copper gluconate) in milk (5.5 mg Cu/kg/day) and adult monkeys exposed via feed (7.5 mg Cu/kg/day) did not identify any adverse hepatic effects after 3 years of exposure (Araya et al. 2012). The monkeys were evaluated for serum enzyme activities in blood every 2–3 months and liver biopsies were collected for histopathology every 3–6 months during the study (Araya et al. 2012).

2.10 RENAL

Data regarding renal toxicity of copper inhalation in humans is limited to a single case study. A 2-year-old female who inhaled an unknown amount of a copper powder and spilled some on her facial skin developed renal failure accompanied by oliguria (low urine output) (Donoso et al. 2007).

Renal toxicity was observed in a number of case studies following accidental and intentional ingestion of copper sulfate, the most common effects being elevated serum creatinine, oliguria, hemoglobinuria, and hematuria (blood in urine) (Du and Mou 2019; Franchitto et al. 2008; Gamakaranage et al. 2011; Gupta et al. 2018; Hassan et al. 2010; Lubica et al. 2017; Malik and Mansur 2011; Mortazavi and Jafari-Javid 2009; Shankar et al. 2023; Sinkovic et al. 2008; Sood and Verma 2011; Yadla et al. 2015; Yang et al. 2004). In some cases, renal failure was reported in conjunction with other manifestations of copper toxicity without providing further details on the nature of the renal effects (Valsami et al. 2012; Griswold et al. 2017; Gunay et al. 2006). In addition to oliguria and hemoglobinuria, a 40-year-old man also

developed ketonuria and proteinuria following intentional ingestion of copper-8-hydroxyquinolate (Yang et al. 2004). A 19-year-old woman who intentionally ingested an unknown amount of a pesticide containing copper oxychloride developed chronic renal failure (Gunay et al. 2006).

Congestion of the glomeruli and denudation of tubular cells were observed in four individuals who consumed 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, all 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). No studies were located regarding renal effects in humans following dermal exposure to copper.

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

Some experimental rat studies confirm that the kidney is a target of copper toxicity in cases of copper overload. Increased serum levels of creatinine and blood urea nitrogen (BUN) and renal interstitial bleeding were observed in rats given a single gavage does of 2 mg Cu/kg/day as copper chloride (Husain et al. 2023). Doses of 119 mg Cu/kg/day as copper sulfate given to rats for 1 week resulted in increased serum levels of urea, uric acid, and creatinine, and renal histology that includes destroyed glomerular corpuscles and epithelial lining of the proximal and distal convoluted tubules, and glomerular epithelial hyperplasia (Alharbi et al. 2019). Rats gavaged with 25.5 mg Cu/kg/day as copper sulfate pentahydrate for 2 weeks exhibited increased serum levels of urea, uric acid, and creatinine (Abdel-Baky 2019). However, other acute-duration studies found no renal effects. No kidney related serum chemistry changes were observed in rats administered 888 mg Cu/kg/day as copper oxide in gavage for 3 days (Keshavarzi et al. 2019) and no gross or histological lesions were observed in rats administered 300 mg Cu/kg/day as copper sulfate in the diet for up to 2 weeks (Haywood 1980). An acute-duration study by Kadammattil et al. (2018) reported no significant cellular changes in the kidneys of mice dosed with 4 mg Cu/kg/day as copper sulfate.

Several intermediate-duration studies reported kidney dysfunction, indicated by significantly elevated BUN and creatinine, and histological lesions. Rats exposed for 28 days to gavage doses of 25.5–39.8 mg Cu/kg/day as copper sulfate had increased serum levels of BUN and creatinine and renal lesions of tubular degeneration, necrosis, tubular dilation, and glomerular degeneration (Dai et al. 2020, 2023). Mice exposed to 80 mg Cu/kg/day as copper sulfate via gavage for 28 days had increased serum levels of BUN and creatinine and renal histology of tubular degeneration, dilation, and necrosis (Peng et al. 2020).

Significantly increased urea and creatinine were noted in rats following 30 days of exposure to 50.9 mg Cu/kg/day as copper sulfate pentahydrate (Khushboo et al. 2018). Kumar and Sharma (1987) reported significantly elevated urea levels at 39.8 mg Cu/kg/day as copper sulfate for 30 days. Baali et al. (2023) observed increased serum levels of urea, uric acid, and creatinine in rats exposed to 12.1 mg Cu/kg/day as copper quinolate for 8 weeks. While no changes in kidney weights were observed, histology results include glomerular atrophy resulting in glomerular space dilation, and congestion and hypertrophy of the glomerular chamber, although these lesions were not quantified and were therefore not included in the LSE table. Increased serum levels of BUN were observed in rats exposed to 25.5 mg Cu/kg/day as copper sulfate for 90 days (Kumar et al. 2015). Copper-induced histological changes in the kidneys of male rats exposed to 39.8 mg Cu/kg/day as copper sulfate for 20–90 days included necrosis of the tubules, engorged uriniferous tubules, nuclear pyknosis and cell proliferation in the medullary region, hemorrhage, and glomerular capsule degeneration in the cortex (Kumar et al. 2015, 2016a; Rana and Kumar 1980). Kumar et al. (2016a) observed time- and dose-dependent increased severity of histological damage in rats treated for 30, 60, or 90 days with copper sulfate. The severity score criteria used a 1–5 scale to grade vascular, inflammatory, and cellular degenerative changes in the kidney (Kumar et al. 2016a). Kumar et al. (2016a) reported that the histopathological severity score positively correlated with BUN. In a second study, Kumar et al. (2016b), found a time-related, positive correlation between increased BUN and serum creatinine and free copper levels. Sakhaee et al. (2012) reported renal lesions of mild tubular necrosis and hyaline casts following exposure in rats treated with 39.8 mg Cu/kg/day as copper sulfate for 8 weeks. Additional histological observations included necrosis, degeneration, and desquamation to the epithelial lining of the proximal and distal convoluted tubules in rats exposed to doses up to 199 mg Cu/kg/day as copper sulfate (Alharbi et al. 2019; Haywood 1980; Seven et al. 2018). Rats fed up to 12.7 mg Cu/kg/day as copper chloride, exhibited glomerular swelling and proliferation of interstitial cells; however, the incidence and severity of these histological results was not quantified and thus were not included in the LSE table (Wan et al. 2020). Increased relative kidney weights were also noted at 12.7 mg Cu/kg/day but in the absence of body weight or absolute kidney weight data, the relevance is unclear.

NTP (1993) evaluated copper sulfate pentahydrate exposure in drinking water and diet to rats and mice for 2 or 13 weeks. Renal effects observed in rats fed 92–93 mg Cu/kg/day as copper sulfate for 15 days include increased protein droplets in cortical tubules in male and female rats (NTP 1993). Increases in serum levels of BUN and an increase in cortical tubule protein droplets in the proximal tubule were observed in rats fed 17 mg Cu/kg/day as copper sulfate for 13 weeks (NTP 1993). However, NTP (1993) reported no renal effects in mice of both sexes exposed to 24–36 mg Cu/kg/day in water or 717–781 mg Cu/kg/day in the diet for 15 days or in mice fed 815–1,058 mg Cu/kg/day in feed for 13 weeks.

No kidney-related changes in serum chemistry parameters, urinalysis, kidney weights, or histopathology were observed in rats given 51 mg Cu/kg/day as copper chloride via gavage for up to 38 days in a combined repeat-dose and reproduction/developmental toxicity screening study (Chung et al. 2009).

2.11 DERMAL

Information regarding dermal effects in humans following copper inhalation is limited to one occupational study. Impregnation of the squamous nasal epithelium and nails with colored copper deposits was seen in 44 workers involved with grinding and sieving of copper dust (Suciu et al. 1981). These workers made up more than half of the studied workers (Suciu et al. 1981). Forty-three workers had fissured palmo-plantar hyperkeratosis. The workers had been exposed to declining concentrations (from 464 to 111 mg Cu/m^3) over a 3-year period, but the study authors did not evaluate changes in dermal condition prevalence over this time period (Suciu et al. 1981).

Several case studies reported dermal effects in humans following intentional and accidental ingestion of copper substances, including copper sulfate, copper oxychloride, and copper-8-hydroxyquinolate. Reports of skin discoloration in human case studies following copper ingestion used descriptive terms such as mauve lavender (Sood and Verma 2011), yellow (Du and Mou 2019), and green (Yadla et al. 2015). Pallor was reported in conjunction with cyanosis or other skin discoloration in two cases (Malik and Mansur 2011; Yadla et al. 2015) and reported as the only observed dermal effect in two cases (Gunay et al. 2006; Mortazavi and Jafari-Javid 2009).

Second-degree chemical burns were reported in two cases following dermal exposure to copper. One case was a 53-year-old man who developed severe burns and cyanosis after spilling a hot copper sulfate solution on his leg; however, the burns may have been physical in origin (due to temperature) rather than chemical (Park et al. 2018). Copper sulfate solutions are not usually regarded as caustic (causing chemical burns). Another case was an 11-year-old girl who developed burns on her hands with bilateral cellulitis after a blue substance, later identified as copper sulfate, was deliberately applied to her hands in a traditional healing ceremony (Lapid 2008).

One case report documented contact urticaria in a 22-year-old man after dermal exposure to copper (Seki et al. 2021). The man developed a rash on his wrists after using an electric file to shave a copper plate.

Subsequent skin prick testing with copper sulfate solution at a dermatology office yielded positive results, while patch testing was negative (Seki et al. 2021).

Dermal effects have been recorded after injection exposures to copper. A 22-year-old man developed yellow skin discoloration after intentionally injecting approximately 1 g copper sulfate intravenously (Behera et al. 2007). A 41-year-old woman developed necrotic tissue surrounding injection sites after intentionally injecting 2.5 g copper glycinate subcutaneously (Oon et al. 2006).

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

Data on dermal effects in animals following oral exposure to copper are limited to a single study in rats exposed daily to 50.9 mg Cu/kg/day as copper sulfate for 30 days, in which rough, dry skin with alopecia, most notably on the skin of the abdominal region, was reported (Khushboo et al. 2018).

No dermal effects were seen in rats dermally exposed to doses up to 1,000 mg/kg/day copper 8-quinolinolate for 4 weeks in an unpublished study submitted to EPA and reviewed by EPA (2021a).

2.12 OCULAR

Very few reports of ocular effects after copper exposure were located. Kayser-Fleischer rings (excess copper deposits in the cornea) are a common finding in patients with Wilson's disease (Rodriguez-Castro et al. 2015). Eye irritation was reported by factory workers exposed to copper dust (Askergren and Mellgren 1975). A 64-year-old man developed a corneal ulcer with gradual vision loss and pigment discoloration in his left eye 3 years after retiring from a job where he handled copper wire regularly (Cai et al. 2009). It was suspected that a small piece of copper wire was lodged in his eye, causing the ulcer and vision loss.

No animal studies examining ocular effects following inhalation, oral, or dermal copper exposure were located.

2.13 ENDOCRINE

Seven cases of enlargement of the sella turcica and nonsecretive hypophyseal adenoma, accompanied by obesity, arterial hypertension, and "red facies" were observed in a group of 100 workers exposed to 111–

464 mg Cu/m^3 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 (Suciu et al. 1981); however, neither the significance of this effect nor its relationship to copper exposure can be determined.

Three case studies reported endocrine effects in humans following intentional ingestion of copper sulfate. A 26-year-old man developed acute pancreatitis after intentionally ingesting approximately 30 g copper sulfate (Gamakaranage et al. 2011). A 53-year-old man also developed acute pancreatitis after intentionally ingesting 120 g copper sulfate (well above reported lethal doses); medical intervention prevented death (Lubica et al. 2017). A 33-year-old woman developed adrenal insufficiency with reduced cortisol after intentionally ingesting an unknown amount of copper sulfate (Sinkovic et al. 2008). In all cases, the endocrine effects were not permanent, and the patients made full recoveries within weeks. No studies were located regarding endocrine effects in humans following dermal exposure to copper.

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

Oral studies in animals consistently showed no evidence of endocrine effects. Rats exposed to up to 20 mg Cu/kg/day as copper monochloride for 30 days had no treatment-related changes in adrenal, thyroid, or pituitary gland weights or histopathology (Chung et al. 2009). No histological differences were observed in the adrenal, parathyroid, or pituitary glands of rats exposed to copper sulfate at doses as high as 31–36 mg Cu/kg/day in water or 285–324 mg Cu/kg/day in feed for 15 days (NTP 1993). Similarly, no differences in these measures were seen in mice exposed to doses as high as 24–62 mg Cu/kg/day for 15 days in water (NTP 1993). Additionally, no effects were observed in the same study in rats exposed to dietary doses of up to 134–140 mg Cu/kg/day or in mice exposed to dietary doses as high as 815–1,058 mg Cu/kg/day for 13 weeks (NTP 1993).

2.14 IMMUNOLOGICAL

A controlled exposure study in humans exposed to copper-containing welding fumes reported a significant increase in blood C-reactive protein (Markert et al. 2016). Men were exposed to 0.41 mg Cu/m^3 in a copper-only (zinc-free) welding fume for 6 hours/period, for 3 periods with 1 week between exposure periods. Welding fumes were generated in a separate room and were connected by a ventilation system to the room where subjects were exposed (Markert et al. 2016). The change in C-reactive protein was <1 mg/L relative to control subjects (control data were published in an earlier study) and absolute

mean values were not reported, so it is uncertain whether the increased C-reactive protein was clearly adverse. Several similar experiments evaluating inflammatory markers and respiratory function were conducted by the same laboratory (Krabbe et al. 2019, 2023; Reisgen et al. 2020), but these used zinc- and copper-containing welding fume which contained ~60% zinc and ~20% copper. As a result, it is not possible to discern effects from copper itself in these experiments.

In a birth cohort in the Netherlands, increased risk of allergic sensitization was positively associated with modeled estimates of copper in airborne PM_{10} in children's current home address (Gehring et al. 2015). Copper in particulate matter was not associated with incident asthma, asthma symptoms, hay fever, or rhinitis (Gehring et al. 2015).

Immunological effects were evaluated in a controlled exposure study in which nine men were exposed to copper in their food (Turnlund et al. 2004). The experiment began with an 18-day period during which the men consumed a controlled diet providing 1.6 mg Cu/day while residing in a metabolic research unit. At the end of that period, the subjects resumed their normal diets at home and took supplements containing 7 mg Cu/day as copper sulfate for 129 days, followed by a second 18-day residential period in the metabolic research unit during which they received a controlled diet providing 7.8 mg Cu/day (Turnlund et al. 2004). The study authors did not report the dietary copper level during the intervening 129 days, so dose levels across the entire exposure period could not be reliably estimated and effect levels could not be determined. Blood samples collected at the end of each 18-day residential period were analyzed for white blood cell, polymorphonuclear (PMN) cell, and lymphocyte counts; immunoglobin G; and interleukins 2R and 6 (IL-2R and IL-6). During the second 18-day period of exposure, the men had significantly lower PMN cells and higher lymphocytes, as well as significantly lower IL-2R levels when compared with the results from the first 18-day period (Turnlund et al. 2004). The study authors also evaluated antibody titer after the men received a trivalent influenza vaccine. The timing of the vaccinations was inconsistently reported in the publication, and it is not clear whether the vaccines were administered during the 129-day "free-living" period or during the second 18-day residential period. Blood was collected for antibody titers before immunization and 14 days after immunization and compared with results for a similarly immunized control group of 10 subjects who did not receive copper supplements (Turnlund et al. 2004). The copper-exposed subjects exhibited smaller increases in antibody titers to all three influenza strains compared than controls (controls showed 32–92-fold increases from pre-immunization titers, while exposed subjects showed 12–14-fold increases), although the difference was statistically significant for only one strain (Turnlund et al. 2004).

Case reports documenting immune system effects in humans are limited. Reduced albumin and globulin were observed in a 17-year-old boy who ingested 10 g copper sulfate (Du and Mou 2019). Eife et al. (1999) reported that, among 29 patients with chronic copper poisoning from plumbing, one had a natural-killer cell deficiency. Copper levels in tap water measured in homes of these patients ranged from 0.1 to 16.9 mg Cu/L (Eife et al. 1999).

In some individuals, exposure to copper metal produced 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; Seki et al. 2021). Axillary lymphadenopathy was reported in an 11-year-old boy who had copper sulfate crystals intentionally applied to his hands (Lapid 2008).

An acute-duration inhalation study in mice reported an impaired immune response in host defense assays following inhalation exposure to copper sulfate (Drummond et al. 1986). The study authors reported exposure concentrations both in terms of sulfate (mg SO_4/m^3) and in terms of "calculated mg metal/m^3." However, the reported copper concentrations were inconsistent with the concentrations reported in terms of sulfate[4]. This apparent error was limited to the copper concentrations, as the aluminum concentrations reported as "mg metal/m^3" for aluminum sulfate compounds in the study were consistent with the corresponding sulfate concentrations. Because of the error, the copper exposure concentrations are uncertain and effect levels cannot be determined for the study. In the study, increased mortality and decreased survival time were observed in CD-1 mice challenged by an aerosol of *Streptococcus zooepidemicus* following 0.56 mg Cu/m^3 for 3 hours or 0.13 mg Cu/m^3 for 3 hours/day, 5 days/week for 2 weeks. Decreased bactericidal activity of alveolar macrophages was also observed in mice exposed to 3.3 mg Cu/m^3 for 3 hours or 0.12 mg Cu/m^3 for 3 hours/day, 5 days/week for 2 weeks following exposure to an aerosol of *Klebsiella pneumonia* (Drummond et al. 1986). There were no functional differences in macrophages in rabbits exposed to 0.6 mg Cu/m^3 as copper chloride for 6 hours/day, 5 days for 1 month (Johansson et al. 1983).

Only one study of immune system effects following acute-duration oral exposure to copper in animals met inclusion criteria. In mice, a 7-day exposure to copper sulfate at doses between 1 and 4 mg Cu/kg/day resulted in follicular hyperplasia in the spleen (Kadammattil et al. 2018). Incidences and

[4]For example, Drummond et al. (1986) reported one copper sulfate exposure level as 2.53 mg SO_4/m^3 and 3.3 "mg metal/m^3." However, the copper concentration corresponding to 2.53 mg SO_4/m^3 would be 1.67 mg Cu/m^3.

severities of the lesion were not reported by Kadammattil et al. (2018), precluding identification of effect levels for the spleen.

Intermediate-duration oral studies of spleen weight and histopathology had mixed results. No histopathological changes were seen in the spleens of rats exposed to doses as high as 31–36 mg Cu/kg/day as copper sulfate in drinking water or as high as 285–325 mg Cu/kg/day as copper sulfate in feed for 15 days (NTP 1993). However, rats exposed for 30 days to 50.9 mg Cu/kg/day as copper sulfate showed congested and enlarged spleens (Khushboo et al. 2018).

In rats exposed to 199 mg Cu/kg/day as copper sulfate for 21 days, serum tumor necrosis factor-alpha (TNF-α) levels were increased 1.55 times greater than in controls, but no other evidence of inflammation was examined (Seven et al. 2018). Decreased white blood cell counts of 42% were observed in female rats given 39.8 mg Cu/kg/day as copper sulfate for 5 weeks (Adele et al. 2023). There were no effects on spleen weight or histology in rats exposed to up to 51 mg Cu/kg/day as copper chloride for ~35 days (Chung et al. 2009). A 19-week study in mice exposed to 22 mg Cu/kg/day as copper sulfate showed altered phenotypic properties of immunocompetent cells as evidenced by decreased percentage of suppressor (CD8+CD4), natural killer (NK) and NK precursor (CD4+CD8+) cells, and increased immunoregulatory index (helper to suppressor ratio) (Kvietkauskaite et al. 2004).

Two unpublished studies submitted to EPA and reviewed by EPA (2021a) reported immunological effects of copper 8-quinolinolate. In a 90-day study of rats exposed via diet, females exhibited increased spleen weight at doses ≥100 mg/kg/day copper 8-quinolinolate. In the other study, male rats exposed dermally to 1,000 mg/kg/day copper 8-quinolinolate for 28 days had an increased incidence of necrosis in the thymic lymphocytes. EPA (2021a) did not provide additional information on these findings.

2.15 NEUROLOGICAL

Studies in workers exposed by inhalation and case reports of humans exposed orally to copper have reported neurosensory effects, and some epidemiological studies have suggested effects of excess dietary copper on cognition and/or memory. While robust human data to support a relationship between excess copper exposure and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases are lacking, there are mechanistic data suggesting the possibility that copper may play a role; these data are discussed in Section 2.21, Mechanisms of Toxicity. Neurobehavioral changes have been reported in

animal studies of oral exposure to copper, and at high oral doses (≥25.5 mg Cu/kg/day), copper has been shown to induce neuromuscular effects in laboratory animals.

Neurological effects in humans following copper inhalation were reported in an occupational health study and one case report. Headache, vertigo, and drowsiness were reported in factory workers exposed for 3 years, beginning with a maximum concentration of 464 mg Cu/m^3 and declining over 3 years to 111 mg Cu/m^3 copper dust (Suciu et al. 1981). The prevalence of neurological symptoms declined with declining exposure concentrations (Suciu et al. 1981). A 2-year-old girl who accidentally inhaled copper dust experienced sensory impairment within the first few hours of exposure (Donoso et al. 2007).

Seven adult females exposed to 0.07 mg Cu/kg/day as copper sulfate for 2 weeks in a controlled exposure study experienced headaches (Pizarro et al. 1999). Neurological effects following ingestion of copper substances, including copper sulfate, copper oxychloride, and copper-8-hydroxyquinolate, were also reported in several case reports. The most common effects were headache, dizziness, agitation, and drowsiness (Du and Mou 2019; Gunay et al. 2006; Malik and Mansur 2011; Yang et al. 2004). Dizziness after oral exposure to copper may stem from stimulation of gastrointestinal tract receptors that can alter the brain response to vestibular stimulation (Yates et al. 2014).

Epidemiological investigations of neurological effects in humans exposed to copper in the diet have been conducted; those that met inclusion criteria (see Appendix C, Section C.2.2) are shown in Table 2-8. A large (>10,000 subjects) prospective cohort study of adults in the United States showed an association between an increase in dietary copper intake of 1 mg Cu/day and an increased risk of incident dementia (hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.04, 1.95) among participants whose diets were high in saturated fat, but not among those whose diets were not high in saturated fat (Wei et al. 2022). The study authors also observed an association between dietary copper intake and a decline in scores on word fluency tests (over the 20-year follow-up) in both groups. Dietary intake was estimated at enrollment in the cohort (1987–1989) and again a few years later (1993–1995) based on responses to a validated food frequency questionnaire administered by an interviewer. Cognitive assessments were performed at three time points; the first time point, 1996–1998, served as the baseline assessment. The study authors noted several strengths of their study, including the large sample size, long follow-up, and prospective cohort design (Wei et al. 2022). Limitations highlighted by Wei et al. (2022) included their inability to account for copper intake from water or other local sources and the limited number of cognitive tests administered.

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Copper and Neurological Effects

Reference, study type, and population	Exposure	Outcome evaluated	Result
Odai et al. 2020 Cross-sectional, 245 women >40 years of age visiting menopause clinic (Japan)	Estimated dietary intake based on questionnaire: 0.15 mg Cu/MJ among women 40–54 years old	Severity of subjective forgetfulness	↔
	0.17 mg Cu/MJ among women ≥55 years old	Severity of subjective forgetfulness	↑
Wang et al. 2021 Cross-sectional, 2,483 adult participants (~50% male, ≥60 years of age) in NHANES (2011–2014) (United States)	Estimated dietary intake based on 24-hour recall: 1.2 mg Cu/day (mean)	Cognitive function scores (word list recall, animal fluency, and digital symbol substitution tests)	↔ for intake >RDI
Wei et al. 2022 Prospective cohort, 10,269 participants (~44% male, mean age 62.9 years old) in Atherosclerosis Risks in Communities Study in four states (United States)	Estimated dietary intake from food and supplements: 1.25 mg Cu/day (mean)	Incident dementia among participants with high intake of saturated fat	↑
		Scores on word fluency test	↓

↑ = association; ↓ = inverse association; ↔ = no association; MJ = millijoule energy; NHANES = National Health and Nutrition Examination Survey; RDI = recommended dietary intake

Other studies that met inclusion criteria were cross-sectional in design, so temporality of the association cannot be established. A small cross-sectional study of women visiting a menopause clinic in Japan reported an association between increased severity of subjective forgetfulness and estimated dietary copper intake among those ≥55 years of age, but not among those between 40 and 54 years of age (Odai et al. 2020). In a cross-sectional study of 2,483 adults at least 60 years old who participated in NHANES (2011–2014) surveys, no significant association was seen between scores on tests of cognitive function and copper intake when estimated dietary intake was greater than the recommended dietary intake (Wang et al. 2021).

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

No treatment-related changes in brain weight or brain histopathology were observed in rats exposed to dicopper oxide by whole-body inhalation at concentrations up to 1.76 mg Cu/m^3 for 4 weeks (Poland et al. 2022). No other studies of neurological effects in animals exposed by inhalation were located.

Neurological effects after oral exposure to copper (as copper sulfate or copper monochloride) were studied in acute and intermediate-duration studies. No histological changes were observed in the brains of mice exposed to doses up to 4 mg Cu/kg/day as copper sulfate for 7 days (Kadammattil et al. 2018). In 15-day exposure studies, no compound-related changes in brain weight or histology were seen in rats after exposure up to 29 mg Cu/kg/day in drinking water or up to 324 mg Cu/kg/day in food or in mice exposed up to 36 mg Cu/kg/day in drinking water or up to 294 mg Cu/kg/day in food in the form of copper sulfate (NTP 1993). In the longer-duration 13-week study, gliosis in the brain was seen in 10/10 female rats exposed to 134 mg Cu/kg/day as copper sulfate in food, but not at 68 mg Cu/kg/day. No neurological effects were observed in male rats exposed up to 140 mg Cu/kg/day or mice exposed to up to 267 mg Cu/kg/day for 13 weeks in food (NTP 1993). Also, rats gavaged with up to 51 mg Cu/kg/day as copper monochloride for 4–5 weeks had no change in brain weight or histology (Chung et al. 2009).

Multiple neurobehavioral effects were observed in rats exposed for intermediate durations. Changes including decreased passive avoidance response (refraining from an act or response that would produce an aversive stimulus), increased immobility time in a forced-swim test, decreased locomotor activity in open field test, and signs of increased anxiety (decreased entries in an open-arm test and decreased exploration time) were observed in rats exposed for 16 weeks to ≥2.6 mg Cu/kg/day as copper sulfate pentahydrate via gavage (Kumar et al. 2019) or 8 mg Cu/kg/day as copper sulfate (Patwa et al. 2022). The rats also exhibited impaired muscle strength and coordination in the rotarod test. The severity of the neurotoxic effects increased with dose (Kumar et al. 2019). Increased depression-like behaviors (assessed in the tail suspension test and forced swim test) and degeneration of neurons in the prefrontal cortex, hippocampus, and striatum were observed in rats following exposure to ≥10 mg Cu/kg/day as copper sulfate for 28 days via gavage (Adeleke et al. 2023). Impaired learning and spatial memory and recognition were also observed in rats following 28 days of exposure to 0.2 mg Cu/kg/day via gavage (Kaur et al. 2021). However, this study was not included in LSE table or figure because the estimated dose is below the recommended dietary intake of copper in rats, and no information on dietary or water copper levels were reported to ensure that the animals' intake was adequate. A feeding study in rats exposed to 23 mg Cu/kg/day as copper sulfate in the diet for 30 days reported no effects on spontaneous motor activity (assessed using an actophotometer), learning ability (assessed using a pole climbing chamber), or relearning capacity and memory (assessed using a Y-maze) (Murthy et al. 1981). The same study

observed 16 and 17% increases in brain levels of dopamine and norepinephrine neurotransmitters, respectively, when the rats were given copper with a high-protein diet (21% casein), but no change when the rats received copper with a low-protein diet (10% casein). De Vries et al. (1986) did not find significant alterations in corpus striatal dopamine levels in rats exposed to 46 mg Cu/kg/day as copper sulfate in drinking water for 11 months. However, a 25% decrease in the levels of a dopamine metabolite, 3,4-dihydroxyphenylacetic acid, in the corpus striatum was observed.

Serious neurotoxic effects observed in rats exposed to a dose of 25.5 mg Cu/kg/day as copper sulfate (by gavage) included impaired motor coordination, cognitive function, and changes in locomotor activity (Kalita et al. 2020; Kumar et al. 2015). Toxicity was demonstrated by reductions in grip strength, fall time latency on a rotarod test, distance traveled, time moving, attention scores, and an increase in resting time (Kalita et al. 2020; Kumar et al. 2015). Changes in grip strength, and rotarod and Y-maze tests results were observed in rats exposed to ≥39.8 mg Cu/kg/day for 30–90 days; neurotoxicity increased with dose (Kumar et al. 2016b). In a similarly designed study by Kumar et al. (2016b), gliosis, pyknotic nuclei, and glial nodule formation in brain sections of rats were observed with doses of ≥39.8 mg Cu/kg/day for 60–90 days. More severe histological findings of neuronal loss and vacuolated spaces marked by depletion of myelin at 79.6 mg Cu/kg/day for 60–90 days were observed in a second study by the same study authors (Kumar et al. 2016a). Severe impairment of spatial learning and memory in the Morris water maze test along with histopathological changes in the cortex and hippocampus (pyknotic hyperstaining, hyperemia, edema, and vacuoles) were seen in rats exposed to 80 mg Cu/kg/day as tribasic copper chloride for 12 weeks via gavage (Yu et al. 2023). Degenerated neurons and focal areas of necrosis in the cerebellum, as well as decreases in acetylcholinesterase (AChE) activity were reported in rats exposed to 79.6 mg Cu/kg/day as copper sulfate for 7 weeks, 3 times/week via gavage (Arowoogun et al. 2021). A study that only tested one dose (50.9 mg Cu/kg/day as copper sulfate) in rats for 30 days reported that copper toxicity slowed brain activity and produced a swollen, congested, and edematous brain (Khushboo et al. 2018). This study was not included in LSE table or figure because the exposed group had a 40% lower water intake and a 30% lower food intake than controls. Effects reported may have stemmed from dehydration and/or malnutrition.

In mice, impaired spatial memory in the Y-maze test and increases in brain AChE activity were seen after exposure to 39.8 mg Cu/kg/day as copper sulfate for 28 days (Isibor et al. 2022). Impaired cognitive function in the Morris water maze test and neuronal degeneration were seen in mice exposed for 90 days to ≥15 mg Cu/kg/day in drinking water (Zhang et al. 2023a). This study was not included in the LSE

table or figure because copper-exposed groups had decreased water intake (20–45% compared to control); dehydration may have been a contributing factor to the effects.

2.16 REPRODUCTIVE

In an occupational health study, sexual impotence was reported in 16% of workers (75–100 workers examined) exposed to copper dust (declining over time from 464 to 111 mg Cu/m^3) during grinding and sieving operations (Suciu et al. 1981). The significance of this finding is difficult to assess because the study did not evaluate whether the prevalence of impotence changed with declining exposure concentrations. No studies were located regarding reproductive effects in humans following oral or dermal exposure to copper.

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

Many animal studies have examined the reproductive toxicity of copper following acute-duration oral exposure. Acute-duration exposure in male rats resulted in decreased serum total testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and/or prolactin following gavage dosing with 25.5 mg Cu/kg/day as copper sulfate pentahydrate for 2 weeks (Abdel-Baky 2019) or 39.8 mg Cu/kg/day as copper sulfate for 7 days (Sarawi et al. 2022). Sarawi et al. (2022) also reported degeneration of seminiferous tubules, loss of spermatogenic series, and an absence of mature spermatozoa in the testes of copper exposed rats. In mice, no changes in testis weight, sperm count, or percentage of abnormal sperm were seen 35 days after a single gavage dose of 4.0 mg Cu/kg/day as copper sulfate (Kadammattil et al. 2018). However, infertility was reported in male mice after 2 weeks of exposure to 6.4 or 8.9 mg Cu/kg/day as copper sulfate pentahydrate via gavage (Al-Musawi et al. 2022). After the 2-week exposure period ended, males were mated with unexposed females until a copulation plug or vaginal sperm was present. No births occurred; histological examination of the testis suggests defective spermatogenesis and death of germ cells occurred in exposed males (Al-Musawi et al. 2022). Female mice exposed to ≥39.8 mg Cu/kg/day as copper sulfate for 14 days had a decrease in the number of antral follicles and ovarian cell damage (Babaei et al. 2012). No differences in number of implantation sites, percentage of viable embryos, or reabsorbed embryos were seen in pregnant mice exposed on GDs 7–12 to 4.0 mg Cu/kg/day as copper sulfate (Kadammattil et al. 2018).

Multiple studies in male rats and mice exposed to copper for intermediate durations suggest that copper plays a role in spermatogenesis and male infertility. Decreases in testicular weight, sperm count, motility, and viability and increases in abnormal sperm morphology were seen in rats exposed to 8 mg Cu/kg/day, as copper sulfate for 24 weeks via gavage; no change in serum testosterone was seen in these rats (Gupta et al. 2021). Similarly, decreases in sperm concentration, count, motility, and viability were observed in rats exposed to ≥39.8 mg Cu/kg/day as copper sulfate for 30–56 days (Liu et al. 2016; Sakhaee et al. 2012); decreases in serum LH and FSH were also seen on one of these studies (Liu et al. 2016). The severity of reproductive toxicity in male animals was found to be dose-dependent in these studies (Liu et al. 2016; Sakhaee et al. 2012). Additionally, at the highest dose tested (79.6 mg Cu/kg/day as copper sulfate), a significant increase in the sperm malformation rate and a decrease in testosterone were noted (Liu et al. 2016). In a separate study in rats by Babaei and Abshenas (2013), significantly decreased sperm count, percentage of live spermatozoa, sperm motility, and testicular weight were seen after 56 days of exposure to 79.6 mg Cu/kg/day as copper sulfate, but not after 28 days of exposure. The signs of reproductive toxicity reported at lower doses were also present in several studies that tested a single higher dose, such as 50.9 mg Cu/kg/day in rats for 30 or 90 days (Arafa et al. 2019; Khushboo et al. 2018), and 127 or 128 mg Cu/kg/day as copper sulfate pentahydrate for 21 days (Parlak Ak et al. 2021; Seven et al. 2020). These effects included significant reductions in testicular weight, testosterone levels, significant increases in sperm head and tail abnormalities, degeneration of epididymides, and testicular degeneration (Arafa et al. 2019; Khushboo et al. 2018). The Khushboo et al. (2018) study was not included in the LSE table or figure because the exposed group had 40% lower water intake and 30% lower food intake, and some effects reported may have stemmed from dehydration and/or malnutrition. No effects on male reproductive organ histology were seen after 15 days of exposure in rats exposed in drinking water (up to 29 mg Cu/kg/day) or diet (up to 324 mg Cu/kg/day) or mice exposed in drinking water (up to 24 mg Cu/kg/day) as copper sulfate pentahydrate (NTP 1993). Thirteen-week feeding studies found no compound-related effects on reproductive organ weights, histopathology, or sperm morphology in rats exposed to doses up to 140 mg Cu/kg/day as copper sulfate or mice exposed up to 815 mg Cu/kg/day as copper sulfate (NTP 1993).

In ICR mice, decreased sperm motility and concentration and increased sperm malformations were seen after 42 days of gavage dosing with ≥3.9 mg Cu/kg/day, and a decrease in testicular weight was seen at ≥7.8 mg Cu/kg/day as copper sulfate (Guo et al. 2021). Chen et al. (2020) reported decreases in epididymal sperm count and motility in CD-1 mice at ≥39.8 mg Cu/kg/day as copper sulfate after 8 weeks of gavage exposure, but not at 10 mg Cu/kg/day. The inconsistent findings may reflect differences in strain of mice; Guo et al. (2021) used ICR mice, whereas Chen et al. (2020) performed their experiment

in CD-1 mice. Significant decreases in sperm concentration, count, motility, and viability were reported in NMRI mice exposed to 39.8 mg Cu/kg/day as copper sulfate once every 2 days for 28–42 days or daily for 42 days via gavage (Sakhaee et al. 2016a, 2016b). In two other studies in male NMRI mice, exposure to 79.6 mg Cu/kg/day as copper sulfate for 42–56 days resulted in changes in sperm parameters similar to those seen in rats, in addition to histological changes including shrinkage and degeneration of seminiferous tubules, moderate to severe degeneration of germinal layers, significantly decreased Sertoli cells nuclei diameter and epithelial height, and significantly less meiotic index (Kheirandish et al. 2014; Sakhaee et al. 2014).

Effects of copper compounds on the female reproductive tract have been reported. In female rats, a 35-day exposure via gavage resulted in changes in ovarian follicular development at ≥6 mg Cu/kg/day as copper sulfate pentahydrate and increases in absolute and relative ovary and uterus weight at ≥12 mg Cu/kg/day (Chen et al. 2023). Changes in ovaries were also seen in mice after a 35-day exposure to copper sulfate at ≥39.8 mg Cu/kg/day (lowest dose tested), including decreases in ovarian follicles and corpora lutea, and structural damage to the ovarian structure (Babaei et al. 2012). Chronic active inflammation of the clitoral gland and ovarian cysts were seen in 10/10 female rats exposed to 134 mg Cu/kg/day as copper sulfate in diet for 13 weeks (NTP 1993). No effects were seen in lower doses of 9–68 mg Cu/kg/day. The NTP (1993) 13-week study in mice reported cysts in the clitoral glands of 8/10 female mice exposed to 1,058 mg Cu/kg/day as copper sulfate in diet and no effects at 52–536 mg Cu/kg/day (NTP 1993). No changes in vaginal cytology were observed in rats or mice (NTP 1993). In 15-day studies, no histological changes in the reproductive organs were reported in female rats exposed up to 26 mg Cu/kg/day as copper sulfate in drinking water or up to 285 mg Cu/kg/day as copper sulfate in food or in mice exposed to 15–36 mg Cu/kg/day in drinking water (NTP 1993).

No reproductive effects were seen in mink exposed up to 13 mg Cu/kg/day as copper sulfate in food for 8 months prior to mating and throughout gestation (Aulerich et al. 1982).

In an unpublished developmental toxicity study of copper hydroxide in rabbits, 2 of 22 pregnant rabbits aborted pregnancies on GD 22 after gavage exposure to 18 mg Cu/kg/day as copper hydroxide; maternal deaths also occurred at this dose (reviewed by EPA 2006). In the EPA (2021a) review of unpublished developmental toxicity studies of copper 8-quinolinolate, reproductive effects were seen in a dose-range-finding study in rabbits exposed orally during gestation. At all doses (≥7 mg/kg/day copper 8-quinolinolate), there were increased pre-implantation losses that led to fewer implantations and live fetuses. However, these results were not confirmed in the definitive rabbit study using doses up to

7 mg/kg/day copper 8-quinolinolate. A two-generation reproductive toxicity study in rats exposed to ≥203 mg/kg/day copper 8-quinolinolate reported decreased numbers of implantation sites in F0 parents, leading to decreased numbers of live F1 pups at birth and on postnatal day (PND 4) (EPA 2021a). No other reproductive effects were seen in this study.

2.17 DEVELOPMENTAL

Only one developmental toxicity study in humans exposed to copper met inclusion criteria (see Appendix C, Section C.2.2): a nested case-control study of 1,172 cases of stillbirth and 7,032 full-term controls in Texas (Rammah et al. 2019). No association was observed between risk of stillbirth and copper concentration in $PM_{2.5}$ modeled for each subject's pregnancy (Rammah et al. 2019). The median modeled copper concentration in $PM_{2.5}$ was 7.06 ng Cu/m^3. No studies regarding developmental effects of humans following oral or dermal exposure to copper met inclusion criteria.

Data on the developmental toxicity of copper in experimental animals are limited. No toxicity studies were identified for developmental effects in animals following inhalation or dermal exposure to copper.

Developmental toxicity following oral exposure to copper has been studied in several species. No significant difference was reported for the number of implantations, nonviable embryos, resorbed embryos, or mean embryo weight when pregnant mice were exposed to 4 mg Cu/kg/day as copper sulfate on days 7–12 of pregnancy as compared to controls (Kadammattil et al. 2018). Rats exposed via gavage 2 weeks prior to mating and throughout gestation to PND 3 with 51 mg Cu/kg/day as copper chloride had litters with increased percentages of runts (defined as weighing at least one-third less than the control means) and pups with icterus, compared to controls (Chung et al. 2009). Decreased litter size and fetal weights were seen when mice were exposed 1 month prior to mating and on GDs 0–19 to ≥208 mg Cu/kg/day as copper sulfate in food (Lecyk 1980). This study was not included in LSE table due to deficiencies in reporting. No developmental effects were observed in the offspring of mink exposed up to 13 mg Cu/kg/day as copper sulfate in food for 8 months prior to mating and throughout gestation (Aulerich et al. 1982).

EPA (2006) reviewed an unpublished developmental toxicity study in rabbits exposed to copper hydroxide. In this study, maternal exposure to 18 mg Cu/kg/day resulted in significantly increased fetal incidences of hemivertebra, delayed ossification (mandible, pelvis, and skull), and supernumerary ribs when compared to the controls; maternal deaths also occurred at this dose. EPA (2021a) summarized the

results of unpublished developmental toxicity studies of copper 8-quinolinolate in rats and rabbits exposed orally during gestation. No developmental effects were seen in rats exposed to doses up to 800 mg/kg/day or in rabbits exposed to doses up to 30 mg/kg/day of copper 8-quinolinolate in guideline (OPPTS 870.3700) studies (EPA 2021a).

Newborn rats exposed on PNDs 7–21 via gavage to ≥0.2 mg Cu/kg/day exhibited changes in serum chemistry and histological changes in the liver; however, this study was not included in the LSE table or figure because the data are inadequately reported to determine an effect level (Dai et al. 2020). No developmental effects occurred in infant guinea pigs exposed to 18.4 mg Cu/kg/day as copper sulfate in water for 6 months (after a month of dosing at 6.6 mg Cu/kg/day in formula milk) (Seffner et al. 1997).

2.18 OTHER NONCANCER

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 Cu/m^3. It has been suggested that other metals present in the workplace could have been the primary causative agents for the metal fume fever, rather than copper (Borak et al. 2000).

One cross-sectional epidemiology study that met inclusion criteria (see Appendix C, Section C.2.2) reported associations between decreased body mass index and waist circumference and estimated dietary intake of copper in 19,952 adult NHANES (2007–2014) participants (Jiang et al. 2020). No other studies of these outcomes met inclusion criteria.

Several experimental oral studies reported reductions in food and/or water intake in animals exposed to copper. In rats fed up to 285–325 mg Cu/kg/day as copper sulfate pentahydrate for 15 days, 37–38% decreased food intake was observed (NTP 1993). Reduced water consumption of 25–67% was observed in mice exposed to doses of 10–62 mg Cu/kg/day as copper sulfate pentahydrate in the drinking water for 15 days (NTP 1993). In rats, decreases in food consumption (by 21–29%) and water intake (41%) were attributed to gavage exposure to 50.9–199 mg Cu/kg/day as copper sulfate for 21–30 days (Khushboo et al. 2018; Seven et al. 2018). Two chronic-duration studies in monkeys reported no differences in food intake following oral intake of 5.5–7.5 mg Cu/kg/day as copper gluconate in diet or milk for 3 years (Araya et al. 2012).

EPA (2006) reviewed an unpublished study of pregnant rabbits exposed to ≥9 mg Cu/kg/day as copper hydroxide on GDs 7–28. The does exhibited significant reductions in mean food consumption accompanied by body weight losses during GDs 7–10.

2.19 CANCER

There are limited data for humans and no data for animals on the carcinogenicity of inhaled copper. Several studies that evaluated the association between lung cancer and exposure to copper in airborne particulate matter or indoor dust measured exposure after the outcome had occurred, and thus were not considered useful for hazard identification. Although a number of studies examined cancer risk among workers at copper smelters, the cancer risk was attributed to arsenic exposure rather than exposure to copper. In a study of >6,700 male workers at a Chinese copper mine, there was a significantly increased risk for cancer (all sites combined) (standardized mortality ratio [SMR] 123, 95% CI 109–139), a significantly increased risk for stomach cancer (SMR 131, 95% CI 105–161), and a significantly increased risk for lung cancer (SMR 147, 95% CI 112–189) (Chen et al. 1993). The cancer risk increased with the duration of employment and time since first exposure (time between first exposure and cancer diagnosis). The risk was also higher in workers employed in the 1950s, when there was a dramatic increase in production, but poor underground ventilation and dry drilling methods were used, which generated high levels of dust. Radon and radon daughters (decay products) were measured in the underground mines; between 1960 and 1990, radioactivity levels of 1.29×10^{-11} Ci/L were recorded. To assess the relative contribution of radon and radon daughters to lung cancer risk, the workers were divided into two groups: underground miners and drilling miners (presumably above ground). Increases in lung cancer risk were observed in both groups, and the study authors suggested that exposure to radiation did not appear to be responsible for the risk of excess death from lung cancer. The copper ore from the Chinese mine also contained silica, iron, manganese, arsenic, titanium, and sulfur (Chen et al. 1993). The study authors noted that the arsenic level in the copper was relatively low (0.061%) and did not likely contribute to the lung cancer risk; however, the lung cancer risk from exposure to silica and iron could not be ruled out. A significant increase in the risk of silicosis was observed in the miners. In a 7-year follow-up of this cohort, Chen et al. (1995) calculated the risks of cancer for: all sites (SMR 129, 95% CI 117–142), stomach cancer (SMR 141, 95% CI 116–169), and lung cancer (SMR 152, 95% CI 123–187). All risks were still significantly elevated. This study also conducted a worker smoking survey and found that a higher percentage of the miners were smokers (71.7%) than the control population of local residents (64.3%). The increased smoking rate, along with the exposures to radioactivity, silica, iron, and arsenic, could have contributed to the increased cancer risk.

No studies were located regarding cancer effects in humans or animals following dermal exposure to copper.

Two oral studies examined the carcinogenicity of copper compounds in animals; however, these studies used only single dose levels, tested small groups of animals (6–13), exposed animals for far less than lifetime, and examined only selected tissues for tumor formation. These studies did not find increases in the occurrence of liver tumors in rats exposed to 130 mg Cu/kg/day as copper acetate for 24 weeks (Kamamoto et al. 1973) or large intestine tumors in rats exposed weekly to 9 mg Cu/kg/day as an unspecified copper compound for 16 weeks (Greene et al. 1987).

In an intermediate-duration study, rats were orally exposed to 62 mg Cu/kg/day as copper gluconate for 6 weeks, and a significant increase in the number of glutathione S-transferase placental form (GST-P) positive single hepatocytes was seen (Abe et al. 2008). There were no changes in number of GST-P positive lesions or area of such lesions (Abe et al. 2008). GST-P-positive foci are considered preneoplastic changes that may progress to neoplasm.

As reported by EPA (2021a), an unpublished carcinogenicity bioassay of copper 8-quinolinolate in mice exposed via diet did not report increased tumor incidences at doses up to 855.8 mg/kg/day copper 8-quinolinolate in males and 1051.7 mg/kg/day copper 8-quinolinolate in females.

Several studies examined the carcinogenicity of copper compounds following parenteral administration. No clear increases in tumor incidence were observed in male Wistar rats receiving subcutaneous injections of 2 mg Cu/kg/day as copper acetate (Yamane et al. 1984); male and female F344 rats receiving intramuscular injections of 0.25 or 0.41 mg Cu/kg/day as finely ground copper (Furst 1971); or Wistar rats receiving intramuscular injections of 150 mg Cu/kg as copper oxide, 150 mg Cu/kg as copper sulfide, or 70 mg Cu/kg as copper sulfate (Gilman 1962). An increase in the occurrence of renal cell carcinoma was observed in male Wistar 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.

IARC has not evaluated the carcinogenicity of copper. IARC lists copper 8-hydroxyquinoline as not classifiable as to its carcinogenicity in humans due to lack of cancer studies in humans and animals (IARC 1987). Neither NTP nor EPA has evaluated the carcinogenicity of copper (IRIS 1988; NTP 2021).

2.20 GENOTOXICITY

Studies investigating the genotoxicity of copper in humans have given inconsistent results. Significant increases in deoxyribonucleic acid (DNA) damage were observed in the peripheral blood leukocytes of males working at a copper smelting plant (duration varied from 0.2 to 25 years) relative to controls, however, these increases were not associated with copper concentrations measured in the blood (De Olivera et al. 2012). Shubber et al. (1998) analyzed blood lymphocytes of women using copper-containing contraceptive IUDs for various periods (1–4 years). Compared to age- and income-matched control women, those using IUDs had significantly higher plasma copper levels and increased frequencies of both chromosomal aberrations and sister chromatid exchanges. In a human study by O'Connor et al. (2003), healthy adults were provided with copper supplements for 6 weeks at doses up to 0.067 mg Cu/kg/day as copper sulfate. There was no evidence of DNA damage to leukocytes. No studies were located regarding genotoxicity in humans after dermal exposure to copper or its compounds.

Several animal studies assessed the genotoxicity of copper sulfate following oral or parenteral exposures and have consistently shown copper to be genotoxic in these systems. The results of these *in vivo* genotoxicity studies are summarized in Table 2-9. Significant increases in the occurrence of micronuclei and chromosomal aberrations have been observed in chick bone marrow cells and erythrocytes 24 hours after exposure to 1.9–2.5 mg Cu/kg as copper sulfate (Bhunya and Jena 1996) and mouse bone marrow cells following exposure to 0.28–8.25 mg Cu/kg as copper sulfate (Agarwal et al. 1990; Bhunya and Pati 1987; Fahmy 2000; Kadammattil et al. 2018; Prá et al. 2008). Peripheral lymphocytes from rabbits gavaged for 6 days with 7.5 mg Cu/kg as copper sulfate showed significant increases in sister chromatid exchanges and chromosomal aberrations (Georgieva et al. 2013). A study of copper sulfate did not find increases in the number of micronuclei in bone marrow cells 24 hours after mice were injected with up to 5.04 mg Cu/kg (Tinwell and Ashby 1990). The discrepancy in findings from other studies is not clear but could be due to differences in mouse strain and/or administration route. Several studies reported DNA strand breaks in blood cells of mice orally exposed to copper sulfate at doses of 0.498–8.5 mg Cu/kg both 24 hours after a single gavage or after 6 days of exposure (Franke et al. 2006; Prá et al. 2008; Saleha Banu et al. 2004). Husain et al. (2021) reported increased DNA strand breaks in intestinal cells after a single oral dose ≥2 mg Cu/kg as copper chloride in rats. DNA fragmentation was also observed in liver cells of rats after oral exposures to 39.8 or 119 mg Cu/kg/day as copper sulfate for 7 days (Alhusaini et al. 2018a, 2018b).

Table 2-9. Genotoxicity of Copper and Copper Compounds *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Non-mammalian systems				
Drosophila melanogaster (oral exposure)	DNA damage	+	Shukla et al. 2011	Copper sulfate
D. melanogaster (injection into larvae)	Recessive lethals	+	Law 1938	Copper sulfate
Mammalian systems				
Human peripheral blood leukocytes (occupational exposure)	DNA strand breaks	–	De Olivera et al. 2012	Copper
Human leukocytes (oral exposure)	DNA strand breaks	–	O'Connor et al. 2003	Copper
Albino rat liver cells (oral exposure)	DNA strand breaks	+	Alhusaini et al. 2018a	Copper sulfate
Albino rat liver cells (oral exposure)	DNA stand breaks	+	Alhusaini et al. 2018b	Copper sulfate
Wistar rat intestinal cells (oral exposure)	DNA strand breaks	+	Husain et al. 2021	Copper chloride
CF1 mice blood cells (oral exposure)	DNA strand breaks	+	Prá et al. 2008	Copper sulfate
Swiss Albino mice leukocytes (oral exposure)	DNA strand breaks	+	Saleha Banu et al. 2004	Copper sulfate
Swiss Webster mice blood cells (oral exposure)	DNA strand breaks	+	Franke et al. 2006	Copper sulfate
Human blood leukocytes (women with copper IUDs)	Chromosomal aberrations	+	Shubber et al. 1998	Copper
Inbred Swiss mice bone marrow cells (i.p. and/or s.c. injection)	Chromosomal aberrations	+	Bhunya and Pati 1987	Copper sulfate
White Swiss mice bone marrow cells (i.p. injection)	Chromosomal aberrations	+	Agarwal et al. 1990	Copper sulfate
New Zealand rabbit blood cells (oral exposure)	Chromosomal aberrations	+	Georgieva et al. 2013	Copper sulfate
White Leghorn chicken bone marrow cells (i.p. injection and oral exposure)	Chromosomal aberrations	+	Bhunya and Jena 1996	Copper sulfate
White Swiss mice spermatocytes (i.p. injection)	Chromosomal aberrations	+	Fahmy 2000	Copper sulfate
Human blood leukocytes (women with copper IUDs)	Sister chromatid exchanges	+	Shubber et al. 1998	Copper
New Zealand rabbit blood cells (oral exposure)	Sister chromatid exchanges	+	Georgieva et al. 2013	Copper sulfate
CBA mice bone marrow cells (i.p. injection)	Micronuclei	–	Tinwell and Ashby 1990	Copper sulfate
CF1 mice bone marrow cells (gavage exposure)	Micronuclei	+	Prá et al. 2008	Copper sulfate
Inbred Swiss mice bone marrow cells (i.p. and/or s.c. injection)	Micronuclei	+	Bhunya and Pati 1987	Copper sulfate

Table 2-9. Genotoxicity of Copper and Copper Compounds *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Swiss Albino mice bone marrow cells (oral exposure)	Micronuclei	+	Kadammattil et al. 2018	Copper sulfate
White Leghorn chicken bone marrow cells (i.p. injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
White Leghorn chicken erythrocytes (i.p. injection and oral exposure)	Micronuclei	+	Bhunya and Jena 1996	Copper sulfate
White Swiss mice bone marrow cells (intraperitoneal injection)	Micronuclei	+	Fahmy 2000	Copper sulfate
Inbred Swiss mice (i.p. injection)	Sperm abnormalities	+	Bhunya and Pati 1987	Copper sulfate
Swiss Albino mice (oral exposure)	Sperm abnormalities	+	Kadammattil et al. 2018	Copper sulfate
White Swiss mice (i.p. injection)	Sperm abnormalities	+	Fahmy 2000	Copper sulfate
ICR mice testis and spleen (gavage)	γ-H2AX levels	+	Guo et al. 2021, 2022a	Copper sulfate

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; IUD = intrauterine device; s.c. = subcutaneous

Sperm abnormalities, including spermatocyte chromosome aberrations, double-headed, and double-tailed sperm, were observed in mice after intraperitoneal exposure to 0.524 mg Cu/kg as copper sulfate for 3 days or 1 mg Cu/kg for 5 days (Bhunya and Pati 1987; Fahmy 2000) and oral exposure to 4 mg Cu/kg as copper sulfate once (Kadammattil et al. 2018). Levels of the DNA damage marker, γ-H2AX, were significantly increased in the testis in mice gavaged with 8.0 mg Cu/kg as copper sulfate for 21 days (Guo et al. 2021). In *Drosophila*, exposure to copper sulfate resulted in significant increases in the occurrence of recessive lethal mutations after 10 minutes (at 0.1% copper concentration) (Law 1938) and DNA damage after 24 hours (at 20 μM Cu) (Shukla et al. 2011).

The results of *in vitro* genotoxicity studies are summarized in Table 2-10. There were no significant increases in the occurrence of reverse mutations in *Salmonella typhimurium* (Marzin and Phi 1985; Tso and Fung 1981; Wong 1988) or *Saccharomyces cerevisiae* (Singh 1983). In contrast, Demerec et al. (1951) found an increased occurrence of reverse mutations in *Escherichia coli*. Positive results were found in studies testing for DNA damage including errors in DNA synthesis using viral DNA polymerase (Sirover and Loeb 1976), a reduction in DNA synthesis in Chinese hamster ovary cells (Garrett and Lewtas 1983), and increased oxidative DNA damage in HeLa cells (Schwerdtle et al. 2007). Occurrence of DNA strand breaks in primary human blood cells following copper exposure has not been consistent. Two studies by Husain and Mahmood (2019, 2020) found that DNA damage occurred in human

lymphocytes at copper concentrations of 0.2–1.2 mM (15–76 mg Cu/L) as copper chloride after 1 hour of exposure, whereas no DNA damage was observed in human CD4+ T lymphocytes exposed to copper at concentrations of 5 mM (318 mg/L) for 48 hours (Caicedo et al. 2008) or human blood cells exposed to up to 40 mM (2.5 g/L) for 30 minutes (Prasad et al. 2006). Several studies conducted in nonprimary human and animal cells have consistently shown increased DNA strand breaks following copper exposure in the absence of activation (Anchordoquy et al. 2017; Dai et al. 2020; Grillo et al. 2010; Jing et al. 2016; Mandil et al. 2020; Schwerdtle et al. 2007; Sideris et al. 1988; Sina et al. 1983; Urbina-Cano et al. 2006). One study reported no change in the number of strand breaks in pulmonary alveolar epithelial cells following a 4-hour exposure up to 24 µg Cu/mL as copper chloride (Boyadzhiev et al. 2022). An increase in sister chromatid exchange in Chinese hamster cells occurred after a 24-hour exposure to 10^{-5}M copper nitrate (Sideris et al. 1988) and is consistent with the clastogenic effects observed in *in vivo* assays. Increased micronuclei formation was observed in rat splenocytes following exposure to 40 µM of copper for 12 hours (Mandil et al. 2020). Unscheduled DNA repair synthesis occurred in rat hepatocytes at copper concentrations of 7.9–78.5 µM, both in the presence or absence of hydroxyurea (Denizeau and Marion 1989).

Table 2-10. Genotoxicity of Copper and Copper Compounds *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms					
Avian myeloblasts virus, DNA polymerase	Errors in DNA synthesis	No data	+	Sirover and Loeb 1976	Copper chloride
Salmonella typhimurium TA 102	Reverse mutation	No data	–	Marzin and Phi 1985	Copper sulfate
S. typhimurium TA98, TA102, TA1535, TA1537	Reverse mutation	–	–	Wong 1988	Copper chloride
S. typhimurium TA100	Reverse mutation	No data	–	Tso and Fung 1981	Copper chloride
Escherichia coli	Reverse mutation	No data	+	Demerec et al. 1951	Copper sulfate
Bacillus subtilis	DNA damage (rec-assay)	No data	–	Nishioka 1975	Copper chloride
Eukaryotic organisms					
Fungi:					
S. cerevisiae	Recombination	No data	–	Sora et al. 1986	Copper sulfate
Saccharomyces cerevisiae	Reverse mutation	No data	–	Singh 1983	Copper sulfate

Table 2-10. Genotoxicity of Copper and Copper Compounds *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Mammalian cells:					
Human blood cells	DNA fragmentation	No data	–	Prasad et al. 2006	Copper chloride
Human lymphocytes	DNA strand breaks	No data	+	Husain and Mahmood 2019	Copper chloride
Human CD4+ T lymphocytes	DNA strand breaks	No data	–	Caicedo et al. 2008	Copper
Human lymphocytes	DNA strand breaks	No data	+	Husain and Mahmood 2020	Copper
Human HeLa S3 cells	DNA strand breaks	No data	+	Schwerdtle et al. 2007	Copper sulfate
HEK293 (human embryonic kidney)	DNA strand breaks	No data	+	Dai et al. 2020	Copper sulfate
Rat hepatocytes	DNA strand breaks	No data	+	Sina et al. 1983	Copper sulfate
Rat splenocytes	DNA strand breaks	No data	+	Mandil et al. 2020	Copper
Mouse Balb-C lymphocytes (comet assay)	DNA strand breaks	+	+	Urbina-Cano et al. 2006	Copper
Mouse primary lymphocytes	DNA strand breaks	No data	+	Jing et al. 2016	Copper
FE1 Mouse pulmonary alveolar epithelial cells	DNA strand breaks	No data	–	Boyadzhiev et al. 2022	Copper chloride
Bovine ovary cells	DNA strand breaks	No data	+	Anchordoquy et al. 2017	Copper
CHO cells	DNA strand breaks	No data	+	Grillo et al. 2010	Copper
Chinese hamster V79 cells	DNA strand breaks	No data	+	Sideris et al. 1988	Copper nitrate
CHO cells	DNA synthesis	No data	+	Garrett and Lewtas 1983	Copper chloride
Chinese hamster V79 cells	Sister chromatid exchange	No data	+	Sideris et al. 1988	Copper nitrate
Rat splenocytes	Micronuclei formation	No data	+	Mandil et al. 2020	Copper
Rat hepatocytes	Unscheduled DNA synthesis	+	+	Denizeau and Marion 1989	Copper sulfate
Human HeLa S3 cells	Oxidative DNA damage	No data	+	Schwerdtle et al. 2007	Copper sulfate
Porcine oocytes	Oxidative DNA damage	No data	+	Chen et al. 2021	Copper sulfate

+ = positive results; – = negative results; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid

Changes in DNA methylation and acetylation caused by exposure to copper can lead to modifications on the epigenome, which could potentially have transgenerational effects. Recent evidence indicates that exposure to copper can influence gene expression by binding to metal response elements and also via epigenetic mechanisms (Cheng et al. 2012). Increased copper levels in the placenta or serum of pregnant mothers have been associated with changes in DNA methylation of placental (Kennedy et al. 2020) and cord blood cells (Weyde et al. 2021). In addition, lower methylation levels of four CpGs sites in blood leukocytes were associated with higher plasma copper concentrations in a Chinese population study (Long et al. 2021). On the other hand, no association was seen between urinary copper levels or pregnant women and DNA methylation in cord blood (Zhang et al. 2022) or between serum copper levels in pregnant women and DNA methylation in peripheral blood cells (Xu et al. 2022). Human cell line and animal studies have been used to demonstrate alterations to the epigenome. Melino et al. (2009) suggested that copper might also modulate histone deacetylase (HDAC) activity in *E. coli* cells, a crucial enzyme in the epigenetic machinery. In another study, rats were exposed to 6.5 mg/kg copper in their feed, which increased DNA methylation (Ognik et al. 2019). No significant trends in global DNA methylation related to inhalation copper exposure in ICR mice were observed (Rossner et al. 2020). Human hepatocyte Hep3B cells treated with Cu^{2+} at 100–200 mM showed significant decreases in global histone acetylation (Kang et al. 2004). Hypoacetylation detected in histones demonstrates that copper is capable of altering the epigenome (Cheng et al. 2012).

2.21 MECHANISMS OF TOXICITY

The molecular mechanisms of copper toxicity were reviewed by Gaetke et al. (2014). Many of the systemic effects of excess copper intake stem from copper's ability to undergo redox cycling, leading to increases in reactive oxygen species and oxidative damage (Gaetke et al. 2014). In cells and tissues, copper exists primarily in the cupric form (Cu^{++}), which can be reduced to Cu^{+} in the presence of reducing agents (e.g., glutathione) or superoxide (Gaetke et al. 2014). The reduction reaction can form hydroxyl radicals, which then catalyze formation of protein and lipid radicals and induce oxidative DNA damage. Evidence from animal studies supports a role for oxidative stress in copper-induced liver, kidney, and neurotoxic effects. Increases in oxidative stress parameters (malondialdehyde, nitric oxide, etc.) and depletion of antioxidants (glutathione [GSH], superoxide dismutase [SOD], catalase) have been demonstrated in the liver (Alhusaini et al. 2018a, 2018b; Hashish and Elgaml 2016; Kumar et al. 2016b; Kvietkauskaite et al. 2004; Liu et al. 2020b; Seven et al. 2018), kidneys (Alharbi et al. 2019; Hashish and Elgaml 2016; Kumar et al. 2016b; Seven et al. 2018), and brain (Behzadfar et al. 2017; Kumar et al. 2016b, 2019) of rats and/or mice exposed orally to excess copper. Kumar et al. (2016a) reported that the

severity of renal histopathological changes in rats exposed to copper correlated positively with malondialdehyde (MDA) levels and inversely with GSH and tacrolimus (TAC) levels in the kidney. Similarly, in rats exposed to 39.8 mg Cu/kg/day for 30–90 days, changes in TAC, GSH, and MDA correlated with functional neurological impairment (Kumar et al. 2016b). Studies of copper-exposed animals concurrently treated with antioxidant preparations (e.g., quercetin, curcumin, *Salvia officinalis* extract) showed mitigation of copper's renal and hepatic effects (Alhusaini et al. 2018b; Dab et al. 2023; Peng et al. 2020), providing further support for the role of oxidative stress.

Several reviews have examined potential mechanisms by which altered copper homeostasis may be involved in the development of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and Lewy body dementia (Aaseth et al. 2021; Acevedo et al. 2019; Coelho et al. 2022; Mezzaroba et al. 2019; Zhang et al. 2022; Zubčić et al. 2020). The redox properties of copper appear to be important because reactive oxygen species lead to both oxidative protein damage and derangements of protein structure (misfolding and aggregation) (Acevedo et al. 2019). Copper interacts with both amyloid and tau proteins that accumulate in the brain in Alzheimer's disease and with alpha-synuclein, which accumulates in patients with Parkinson's disease. For example, in the brain, copper accumulates in amyloid plaques, often associated with extracellular amyloid-β (Aβ) (Acevedo et al. 2019; Zhang et al. 2022). When bound to Aβ, copper redox cycling results in oxidative damage to Aβ, and oxidized Aβ has a higher tendency to aggregate (Acevedo et al. 2019; Wärmländer et al. 2019; Zhang et al. 2022). In addition, high-affinity binding of Cu^{2+} to Aβ peptides induces structural changes that promote aggregation (Acevedo et al. 2019). Copper has also been shown to bind to tau protein, inducing its aggregation, and to accumulate in neurofibrillary tangles characteristic of Alzheimer's disease (Acevedo et al. 2019; Mezzaroba et al. 2019). Similarly, there is also evidence that copper enhances the aggregation of alpha-synuclein (Acevedo et al. 2019; Gaetke et al. 2014; Mezzaroba et al. 2019).

Copper intake has been implicated in neurodegenerative prion diseases such as Creutzfeldt-Jakob disease, as discussed in a review by Oliveri (2023). Prions, misfolded versions of the normal cellular Prion Protein (PrP^C), are able to self-replicate and aggregate in the nervous system and brain. The normal form of the PrP^C is believed to play a role in metal homeostasis, and it has several copper binding sites. Some studies have suggested that copper is involved in the conversion of normal PrP^C to the abnormal form that occurs in prion disease, but further research is needed (Oliveri 2023).

Other potential mechanisms may also be involved in the observed systemic effects of excess copper. In their review, Gaetke et al. (2014) noted that perturbations of copper homeostasis may impair the function

of key catalytic enzymes including cytochrome P450 isozymes through nonspecific binding. Impairment of lipid metabolism, a common finding in Wilson's disease, may be a downstream effect of redox cycling or may occur through altered gene expression. In fish exposed to copper, concentration-related changes in gene expression, including downregulation of cholesterol biosynthesis genes, were observed (Gaetke et al. 2014).

2.22 COPPER NANOPARTICLES

The following section provides a brief overview on toxicity of copper nanoparticles, including copper oxide nanoparticles when indicated, and is focused on highlighting findings from experimental animal studies. Occupational populations are more likely to be exposed to copper nanoparticles than the general population, and emissions may come from industrial facilities such as for asphalt and rubber production (Ameh and Sayes 2019). Copper nanoparticles are also found in pesticides, fertilizers, and personal care products, which may result in its presence in wastewater and sewage (Ameh and Sayes 2019). Crops such as cucumbers or alfalfa can uptake copper nanoparticles from applied agricultural products, and these plants can present another potential source of human exposure (Ameh and Sayes 2019). No epidemiology studies using copper nanoparticles were identified. *In vitro* models using human cell lines have demonstrated that copper nanoparticles induce dose- and time-dependent increases in cytotoxicity, reactive oxygen species, and DNA damage (Alarifi et al. 2013; Karlsson et al. 2008). Research on the effects of copper nanoparticles in animals is limited but suggest that copper nanoparticles may induce a wide range of effects in laboratory animals, as discussed below. Several *in vivo* and *in vitro* studies have demonstrated that copper nanoparticles increase the production of reactive oxygen species and reactive nitrogen species both associated in other studies with serious adverse effects such as genotoxicity, inflammation, apoptosis, and fibrosis (Ameh and Sayes 2019).

The primary target organs for copper nanoparticle toxicity include the liver, kidneys, and spleen. Oral administration of copper oxide nanoparticles can cause significant alterations in the activity of antioxidant enzymes including decreased activity for GSH, catalase, and SOD, plus increases in the lipid peroxidation product, malondialdehyde, at doses as low as 5 mg/kg/day in rats (Anreddy 2018). Hepatic effects in rats and mice resulting from acute- or intermediate-duration oral exposure to copper, copper oxide, or copper carbonate nanoparticles include an enlarged liver; histopathological changes in liver tissues including congestion, hepatocellular degeneration, and steatosis around the central veins of the hepatic tissue; inflammatory responses; increased mitosis; and significantly diminished cytochrome P450 enzyme activities (Chen et al. 2006; De Jong et al. 2019; El Bialy et al. 2020; Lee et al. 2016; Tang et al. 2018).

Oral exposure to copper oxide nanoparticles in mice resulted in increased levels of serum ALT, AST, BUN, ALP, and creatinine. Histopathological effects on the kidneys of rats and mice resulting from exposure to copper nanoparticles include degenerated tubular cells, inflammatory cell infiltration, glomerular hypercellularity, severe coagulative necrosis, detached tubular epithelia, loss of brush border, and narrowing of tubular lumen (Chen et al. 2016; De Jong et al. 2019; El Bialy et al. 2020; Lee et al. 2016). In the spleen, copper nanoparticle exposure resulted in splenic, lymphatic, and thymus atrophy and lymphoid depletion in rats and mice after acute- or intermediate-duration oral exposure (Chen et al. 2016; De Jong et al. 2019; El Bialy et al. 2020; Lee et al. 2016).

Other adverse effects that were observed in animals exposed to copper nanoparticles include evidence for neurological, gastrointestinal, and pulmonary toxicity. Neurotoxic findings following oral or intravenous copper nanoparticle injection in rodents include changes in motor activity and oxidative stress in various brain regions (thalamus, hypothalamus, and medulla), in addition to increasing levels of AChE in the hippocampus and striatum along with decreased exploratory behavior (Fahmy et al. 2020; Luo et al. 2020). In rats and mice, copper nanoparticle exposure altered the cecum microbiome; induced ulcerations in the cecum, colon, and rectum; and caused apoptosis in the duodenum, ileum, and cecum (Cholewińska et al. 2018; De Jong et al. 2019; Luo et al. 2020). A murine pulmonary infection model presents some evidence that copper nanoparticles cause pulmonary inflammation and may reduce lung clearance, thus increasing the risks of pulmonary infections (Kim et al. 2011). No studies to date have directly linked copper nanoparticle exposure to carcinogenicity.

Hematological effects in rats and mice from copper nanoparticle exposure include decreased red blood cell counts, white blood cell counts, hematocrit, and hemoglobin levels (De Jong et al. 2019; El Bialy et al. 2020). Copper nanoparticles appear to affect reproduction in rats and mice as evidenced by decreased sperm count and testes weight in males and decreased FSH, LH, and progesterone in females. Exposure to copper nanoparticles also resulted in ovarian atrophy, disturbance in follicular development, follicular atresia, and reduction in mature follicles (Kadammattil et al. 2018; Yang et al. 2010). Kadammattil et al. (2018) reported that exposure to copper nanoparticles was more toxic to the reproductive functioning of male mice than copper sulfate exposure. Copper nanoparticle exposure resulted in fetal toxicity in rats, including a dose-dependent change in fetal weight, induction of oxidative stress in fetal liver, and increased expression of pro-inflammatory cytokines (Luo et al. 2020).

The toxicokinetics of copper nanoparticles can vary widely depending on particle size, other physicochemical properties, and the preparation. Identified studies were limited to inhalation and

ingestion of copper nanoparticles. A higher rate of aggregation in the brain (direct translocation via the olfactory bulb) was observed than in the gastrointestinal system (as seen with copper) (Naz et al. 2020). Copper homeostasis in the brain is maintained by a coordinated system of copper transporters and chaperones that transport copper across the membranes as required (Haywood 2019). Copper nanoparticles can be distributed throughout the body. The primary target organs in animals tend to be the brain, liver, kidney, and spleen where the copper nanoparticles induce pathological changes and organ injuries. It is hypothesized that the smaller particle size of copper nanoparticles increases surface area, which in turn increases its reactivity with hydrogen ions in gastric fluids. This then enables conversion to ionic copper resulting in increased systemic uptake of copper (Ameh and Sayes 2019). The ionic copper is distributed to the liver with some excreted in bile like other copper compounds. The unabsorbed copper nanoparticles are primarily excreted in the feces of mammals with minimal excretion in urine.

Evidence to date suggests that copper nanoparticles and soluble copper compounds share several target organs including the liver, kidney, and stomach. Specifically, since copper nanoparticles are smaller, they can cross the cellular membrane and induce oxidative injury. In addition, the small particle size also assists them in evading phagocytosis and other immune response mechanisms allowing for translocation to other organs (Chen et al. 2006). The overall database for copper nanoparticles in mammals is limited to a few studies in rats and mice. Most of the copper nanoparticle toxicity studies use *in vivo* and *in vitro* approaches, and most of the toxicity studies thus far focus on aquatic organisms and/or microorganisms (Chang et al. 2012).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Copper is absorbed in the gastrointestinal tract, primarily by the small intestine. Copper absorption ranges from 12 to 71% in adult humans and from 75 to 84% in infants. Dietary copper intake and copper absorption are tightly regulated by copper homeostasis maintenance.
- Following absorption, copper is distributed by a two-phase process. The first phase distributes copper by transport to portal venous circulation where copper is bound to serum protein and ultimately about 75% of this copper is taken up by the liver. In the second phase, copper is bound primarily to ceruloplasmin in the liver, is released to systemic blood circulation, and is redistributed to other organ tissues including the brain, kidneys, muscles, and connective tissues.
- Copper metabolism is largely regulated by copper-transporting P-Type ATPases: ATP7A and ATP7B. Cu(II) reduces to Cu(I) mediated by reductases for copper to transport through cellular membranes.
- Bile excretion through feces is the major excretory pathway for copper. Copper half-lives have been measured in various tissues and were 3.9–21 days in the liver, 5.4–35 days in the kidney, 23–662 days in the heart, and 457 days in the brain.

3.1.1 Absorption

No studies were located that provided data on the rate or extent of absorption following inhalation exposure of copper in humans or animals.

Oral copper absorption occurs in the gastrointestinal tract, primarily in the stomach and small intestine, mostly from the duodenum (van den Berghe and Klomp 2009). Oral absorption was rapid with the maximum concentration of copper in the plasma (C_{max}) detected 1.5 hours after administration of a single gavage dose of 79.5 mg Cu/kg in rats (given as copper gluconate in water) (García-Martínez et al. 2021). Copper is absorbed from the gastrointestinal tract as ionic copper or bound to amino acids. Evidence indicates that oral copper absorption is dependent on transport proteins, particularly the high-affinity copper transport 1 (Ctr1) and ATP7A. Active mechanisms for copper absorption from the small intestine likely initially involve transport through Ctr1 into enterocytes. Prior to uptake across the apical membrane by Ctr1, the oxidized state Cu(II) is reduced to Cu(I) mediated by reductases activity at the apical membrane of the gastrointestinal enterocytes (Nishito and Kambe 2018; Ohgami et al. 2006). Cuprous, Cu(I), copper transported by Ctr1 concentrates in the apical membrane and early endosomes of the intestinal epithelial cells (Nishito and Kambe 2018). From the epithelial cells, copper is then

transported by the copper chaperone, antioxidant-1, to ATP7A that then readily exports copper into the blood of the portal venous system through which distribution occurs (Nishito and Kambe 2018). To maintain homeostasis and regulation of internal copper levels, copper absorption decreases with increased consumption of dietary copper (van den Berghe and Klomp 2009). In a study of adult men fed low-copper or high-copper diets, copper hemostasis was maintained, and absorption was similar between the groups (Harvey et al. 2003). Another study of 11 young men administered various copper doses in food over a period of 42–98 days found absorption efficiencies of 55–56, 36, and 12% at doses of 0.785, 1.68, and 7.53 mg Cu/day, respectively (Turnlund et al. 1989). In humans, the amount of stored copper does not appear to influence copper absorption (Strickland et al. 1972).

Multiple human studies examined the oral absorption of dietary copper and reported absorption rates ranging from 12 to 71% in presumably healthy adults (Harvey et al. 2003, 2005; Jacob et al. 1987; Johnson et al. 1992; Strickland et al. 1972; Turnlund et al. 1982, 1983, 1985, 1988, 1989, 2005; Weber et al. 1969). Peak copper absorption, estimated through a non-compartment analysis, occurred 1–2 hours after ingestion of a single oral dose of copper gluconate in a controlled study of obese males (Boullata et al. 2017). In infants, higher absorption rates were reported, ranging from 75 to 84% (Araya et al. 2003d; Domellof et al. 2009; Olivares et al. 2002).

As previously stated, infants appear to have higher absorption rates than those reported in adults (Araya et al. 2003d; Domellof et al. 2009; Olivares et al. 2002). Olivares et al. (2002) did not find significant differences in copper absorption between 1- and 3-month-old infants. Conversely, Dörner et al. (1989) found a linear relationship between copper intake and retention in a metabolic balance study of infants (aged 2–16 weeks). An animal study by Varada et al. (1993) reported age-related differences in copper absorption which was linear and nonsaturable in suckling (16 days of age) and weanling (21–22 days of age) rats, whereas in adolescent rats (6 weeks of age), copper absorption was saturable. The levels of copper retained in the intestine were greater in the suckling rats than in the weanling or adolescent rats (Varada et al. 1993).

Evidence showing sex and age differences in absorption rate are mixed. Several studies in adults did not find differences in copper absorption between older male and female adults aged 60–83 years (Johnson et al. 1992) or between older men (65–74 years) and young men (22–30 years) (Turnlund et al. 1982, 1988). Conversely, Johnson et al. (1992) did find that copper absorption was higher in women (71%) than in men (64%) aged 20–59 years. Obesity did not appear to impair copper absorption in adult males (Boullata et al. 2017). In addition, the composition of the diet can influence copper absorption including

plant-based protein diets (Turnlund et al. 1983) and lacto-ovo-vegetarian diets through their impacts on the levels of bioavailable copper ions (Hunt and Vanderpool 2001). One study of organic diets did not find an effect on copper absorption (Mark et al. 2013). Organic diets refer to eating crops grown without synthetic herbicides, pesticides, or fertilizers, or without bioengineered genes.

Competition with other metals in the body can also affect copper absorption in humans and animals as iron and zinc are potential absorption inhibitors for copper uptake across cellular membranes. Increased levels of zinc in the diet resulted in decreased in copper absorption in humans and rats (Hall et al. 1979; Hoogenraad et al. 1979; Prasad et al. 1978). Turnlund et al. (1988) found that diets with zinc intake slightly above the RDA did not interfere with copper absorption nor increase fecal copper loss. While absorption significantly varied between study groups (48.1% of radiolabeled copper was absorbed when the diet contained 1.3 mg Cu/day and 16.5 mg Zn/day; 37.2–38.5% of radiolabeled copper was absorbed when the diet contained 1.3 mg Cu/day and 5.5 mg Zn/day), both groups had positive copper balance at both levels. A decrease in copper absorption was observed in infants with high intakes of iron (Haschke et al. 1986). Conversely, iron supplements in healthy breastfed infants at 6–9 months of age had no effect on copper absorption (Domellof et al. 2009). Similarly, in adults with an ileostomy, oral iron therapy given as ferrous gluconate did not appear to impair copper absorption even with increasing doses (Troost et al. 2003).

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 inversely related to cadmium dietary concentration. Conflicting results are 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 bioavailability. However, 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 identified; however, the amount of ceruloplasmin protein was not affected.

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). 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). *Ex vivo* studies on human skin reported mixed results. 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. 1996b). Copper applied transdermally as a tripeptide on *ex vivo* human skin samples permeated the skin and was retained in the stratum corneum, total epidermis, and dermatomed skin (Hostynek et al. 2010). Retention was significant compared to baseline.

3.1.2 Distribution

One study examining respiratory toxicity in rats measured significantly elevated copper levels in the liver and plasma suggesting distribution into these organs (Romeu-Moreno et al. 1994). Nonsignificant increases in copper were measured in kidneys and lung following daily 1-hour inhalation chamber exposure to aerosol copper sulfate for up to 10 days. These results are consistent with more detailed findings of distribution following oral absorption of copper, which is largely similar between humans and animals.

Copper distribution in the body is considered biphasic where ATP7B, predominantly expressed in hepatocytes, is essential for normal distribution of copper. ATP7B has two primary functions: the transfer of copper to a ceruloplasmin that is secreted into the blood and then other organs, and excretion of copper from the body through bile (Guttmann et al. 2018). The first phase is the absorption of copper by enterocytes in the gut and subsequent absorption and distribution by active transport by way of the portal vein (van den Berghe and Klomp 2009). Subsequently, copper levels in the blood rapidly rise as the copper ions bind tightly to albumin and the transcuprin macroglobulin in blood plasma (Moriya et al. 2008). Albumin carries a large portion of the exchangeable copper in peripheral circulation, releasing it to other carriers for cell-specific uptake (Bost et al. 2016; Weiss and Linder 1985). Although passive cellular transport occurs with other metal ions, the absence of copper absorption in Menkes' disease patients and in mice lacking the copper uptake protein, hCTR1, suggest that under normal conditions passive paracellular transport likely does not occur for copper (van den Berghe and Klomp 2009). Prior to phase 1, some copper passes from the small intestines to the large intestines with indigested dietary materials and is then excreted with the feces. A study evaluating plasma kinetics in rats following a single gavage dose of 79.5 mg Cu/kg in rats (given as copper gluconate in water), reported plasma half-life ($t_{1/2}$) and area under the plasma concentration-time curve (AUC) values of 1.79 hours and 2.48 μg/mL*hours, respectively (García-Martínez et al. 2021).

Some dietary copper is transported to the liver where it is bound to ceruloplasmin (a copper-binding serum ferroxide) and released to circulation for distribution. This is the second phase for post-ingestion copper distribution (van den Berghe and Klomp 2009). The maximum concentration of copper in the liver was reached 12 hours after administration of a single gavage dose in rats (García-Martínez et al. 2021). In the liver, hepatocytes are responsible for the uptake, storage, and regulation of copper; about 75% of copper from the portal vein is taken up by the liver and the rest remains in circulation (Harvey et al. 2005). In an *in vitro* experiment using human hepatic (HepG2) and mammary epithelial (PMC42) cells lines, copper was shown to be transported to Ctr1 in hepatic cells by the plasma protein, α_2-macroglobulin (Moriya et al. 2008). 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, binding 60–95% of serum copper (Harvey et al. 2005; Scott and Turnlund 1994). The remaining 10–18% is bound to albumin or carried as amino-acid bound copper and transported into other tissues (Harris 1993; Hellman and Gitlin 2002; Kodama et al. 2012; van den Berghe and Klomp 2009). Copper can also bind to α_2-macroglobulin and small peptides. Regulatory copper proteins ATP7A and ATP7B are responsible for the transport of copper out of cells (reviewed by Taylor et al. 2020). Excessive hepatic copper is transferred from the liver with bile pigments via ATP7B and ultimately excreted with the feces. The brain is the second major site of copper distribution, and copper is also transported to the kidneys, muscle, and connective tissues (Kodama et al. 2012).

Copper crosses the placental barrier and is primarily found in fetal liver in mammals, as part of normal fetal development (Hardman et al. 2007). The fetus obtains copper from maternal serum, either from copper bound to ceruloplasmin, albumin, or anionic amino acids (McArdle 1995). Although copper is found in human breastmilk, it is unclear if it is dependent on maternal plasma copper concentrations (Domellof et al. 2004; Khaghani et al. 2010; Kim et al. 2012). Pre-term infants appear to have lower copper stores than full-term infants (Kim et al. 2012). Intraperitoneal and intravenous exposure to ^{67}Copper or ^{64}Copper in nonpregnant and lactating rats showed that approximately 60% of copper in the lactating rats went directly to the mammary gland (Donley et al. 2002). Copper isotopes also rapidly appeared in milk. The ceruloplasmin in milk is attributed to copper in circulation that reaches the mammary gland. García-Martínez et al. (2021) provided evidence that copper may also cross the blood-brain barrier. Increased copper concentrations were detected in the striatum of rats, with maximum levels measured at 0.25 hours after a single gavage dose of 79.5 mg Cu/kg. Copper concentrations in the midbrain were not altered by oral copper treatment (García-Martínez et al. 2021).

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

3.1.3 Metabolism

Copper metabolism is largely regulated by copper-transporting P-type ATPases ATP7A (also known as Menkes' protein) and ATP7B. Several specific other binding proteins for copper have been identified that are important in the uptake, storage, and release of copper from tissues, most notably ceruloplasmin, which is synthesized in the liver (van den Berghe and Klomp 2009).

In the liver and other tissues, copper is stored bound to metallothionein and amino acids and in association with copper-dependent enzymes. Metallothionein, a metal-binding protein, appears to play an important role in the storage of intracellular copper in a safe compartment and cell survival from both normal and excess copper levels (Tapia et al. 2004). Studies have shown that copper exposure induces metallothionein synthesis which is important for copper homeostasis (Mercer et al. 1981; Wake and Mercer 1985).

STEAP4, a six-transmembrane epithelial antigen of prostate 4, acts as a metalloreductase and is involved in the reduction of Cu(II) to Cu(I), which is necessary for copper transport across the membrane (Scarl et al. 2017). This reduction reaction occurs at the apical membrane of intestinal epithelial cells (Ohgami et al. 2006).

3.1.4 Excretion

No studies were located regarding the rate and extent of excretion of copper following inhalation exposure of humans and animals. The half-time of copper sulfate in the lungs was estimated to be 7.5 hours after intratracheal instillation of 20 μg copper in rats (Hirano et al. 1990).

Bile is the major pathway for the excretion of copper, and primarily excreted in feces. Normally, approximately 2.5 mg Cu/day is excreted in bile (van den Berghe and Klomp 2009). Excessive copper in hepatocytes is excreted into bile from the liver via ATP7B; the reabsorption of biliary copper is negligible as copper binds to components that immobilize it (Farrer and Mistilis 1967; van den Berghe and Klomp 2009). Copper in bile is associated with low molecular weight copper binding components as well as macromolecular binding species (Gollan and Deller 1973). After the oral administration of radioactive

copper as copper acetate in healthy humans, 72% was excreted in the feces (Bush et al. 1955). In six adult men fed ^{63}Cu, 27–46% was excreted in the feces (Turnlund et al. 2005). In humans intravenously administered ^{64}Cu, measurements in feces and urine were negligible (Kjaergaard et al. 2020). In a study in 11 adult men, dietary copper intakes of 0.66, 0.38, and 2.49 mg Cu/day resulted in fecal elimination of 0.65, 0.33, and 2.17 mg Cu/day (Turnlund et al. 1998). A study in rats found an increase in fecal excretion of copper in rats fed a high fiber (potato fiber or sugar beet pulp) diet, likely as a result of reduced copper absorption (Gralak et al. 1996). Bile is also the major excretion pathway in children (Olivares et al. 2002).

Copper excretion in urine is comparatively low relative to fecal excretion, and normal excretion is expected to be 0.01–0.025 mg Cu/day (Bost et al. 2016). In six adult men fed a diet with ^{63}Cu, 1.3–2.1% was excreted in the urine (Turnlund et al. 2005). One study in humans reported that urinary copper excretion in adult females (mean: 18.7 µg/24 hours) was lower than in adult males (mean: 26.2 µg/24 hours) (Vieira et al. 2012).

The half-life of copper in several tissues was calculated by Levenson and Janghorbani (1994). The study sought to understand the processes by which copper was excreted from several tissues. By restricting copper in the diet of rats, the study authors were able to model the competing processes by which the body tends to excrete copper, while concurrently attempting to retain copper for use in other metabolic processes. These were represented as components, where the first component had a relatively rapid half-life generally unaffected by copper dietary restrictions while the second component half-life was increased substantially by a copper restricted diet. The individual half-life component balance for each organ could not be calculated; however, they could be calculated for some organs. The half-lives for each tissue are presented as the component 1 then component 2 half-lives. The respective calculated copper half-lives 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 appeared to be monophasic, with a half-life of 457 days.

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

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and

biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Human PBPK models have been developed for predicting plasma copper levels following intravenous or oral doses of copper (Harvey et al. 2005; Scott and Turnlund 1994).

Harvey et al. 2005 Model

Model Description. Harvey et al. (2005) developed a model for simulating kinetics of copper in humans. The model consists of eight compartments representing plasma (two compartments), liver (two compartments), other tissues, gastrointestinal tract (two compartments), and feces. The two plasma compartments represent copper transferred from the gastrointestinal tract and copper bound to ceruloplasmin transferred from the liver. In the liver, one compartment exchanges copper with the gastrointestinal tract and one transfers copper ceruloplasmin to plasma. The gastrointestinal tract is divided into two compartments, one that delivers copper to plasma, exchanges copper with liver, and receives copper from other tissues; and one that transfers copper to the lower gastrointestinal tract for excretion in feces. Transfers of copper between compartments are simulated as first order and are governed by rate coefficients (day^{-1}), with delay terms applied to transfer of copper ceruloplasmin from liver to plasma and transfer of copper from gastrointestinal tract to feces.

Model Calibration and Evaluation. Parameters consisted of compartment copper masses, inter-compartment rate coefficients and delay terms, and the volume of distribution of the plasma compartment (for comparing observed and measured concentrations). The volume of distribution was assigned a value of 5,000 mL and the transfer rate from the gastrointestinal tract to the compartment destined to deliver

copper to feces was set to 10 day^{-1}. All other parameters were estimated by fitting the model to data collected in a human clinical study (Harvey et al. 2005). In this study, five adult males received an intravenous dose of ^{65}Cu-labelled copper chloride (0.5 mg), and fecal and urine samples were collected over a period or 14 days. Four weeks later, the same individuals received an oral dose of ^{65}Cu-labelled copper chloride (3 mg) after an overnight fast, and plasma, fecal, and urine samples were collected over a period of 14 days. Data from both studies were used to calibrate model parameters. These included plasma and fecal copper (^{65}Cu) following the oral dose and fecal copper following the intravenous dose. The model predicted concentrations of copper in plasma and feces that were within one standard deviation of observations following the oral or intravenous dose (see Figures 2 and 3 of Harvey et al. 2005). The model predicted that approximately 74% of copper absorbed from the gastrointestinal tract is transferred to the liver (first-pass extraction). Of this, 80% is delivered to plasma as copper ceruloplasmin and 20% is secreted back into the gastrointestinal tract (e.g., biliary transfer). Nearly all plasma copper (99%) was predicted to be copper bound to ceruloplasmin. The model was not evaluated with data not used to calibrate parameters.

Scott and Turnlund 1994 Model

Model Description. Scott and Turnlund (1994) developed a model for simulating kinetics of copper in humans. The model consists of seven compartments representing plasma (two compartments), liver (two compartments), other tissues, feces, and urine. The two plasma compartments represent ceruloplasmin and non-ceruloplasmin (other forms of copper). Plasma copper exchanges with copper in liver and other tissues and delivers copper to urine. The two liver compartments represent: (1) non-ceruloplasmin copper received from plasma and transferred to feces and (2) copper ceruloplasmin, which is transferred to plasma. Transfers of copper between compartments are simulated as first order and are governed by rate coefficients (day^{-1}), with delay terms applied to transfer of copper from other tissues to plasma and from liver to feces.

Model Calibration and Evaluation. Parameters consisted of compartment masses, inter-compartment rate coefficients and delay terms and the plasma volume (for comparing observed and measured concentrations). The plasma volume was based on average body-weight-standardized blood volume and hematocrit for humans. All other parameters were estimated by fitting the model to data collected in a human clinical study (Scott and Turnlund 1994). In this study, five adult males were placed on three copper diets that were adequate (1.68 mg/day), low (0.785 mg/day) or high (7.53 mg day), using copper sulfate to supplement the high-copper diet. During each dietary period, the subjects received an

intravenous dose (392 μg) and oral doses of ^{65}Cu-labelled copper chloride (1.02–7.66 mg). Plasma samples were collected at various times during each dietary period. Plasma data (^{65}C) from all dietary periods were used to calibrate model parameters to each subject. The model predicted observed spikes in plasma concentration following intravenous and oral dosing and the concentrations between doses (see Figures 2 and 3 of Scott and Turnlund 1994). The model predicted that 4.1% of the total copper burden was in plasma and that 65% of plasma copper was bound to ceruloplasmin, which was within the range of observations (56–68%). Two rate coefficients were affected by dietary copper levels. The rate of transfer of copper from liver to plasma ceruloplasmin was lower during the low copper period compared to the adequate and high copper periods. The rate of transfer from plasma ceruloplasmin to other tissues increased with increasing dietary copper. The model was not evaluated with data not used to calibrate parameters.

3.1.6 Animal-to-Human Extrapolations

NTP (1993) demonstrated that mice appeared less sensitive than rats to the hepatotoxicity of copper based on the observation that no hepatic effects occurred in mice given doses much higher than rats, which showed liver damage at much lower doses. The cause of this apparent difference in toxicity between the species has not been examined.

The dietary requirements for copper in rats and mice are 5 and 6 mg Cu/kg diet, respectively (corresponding to a dose of ~0.5 mg Cu/kg body weight/day in rats and ~1 mg Cu/kg-body weight/day in mice), (NRC 1995). It is unlikely that humans would tolerate prolonged exposure to a copper dose that is about 40 times higher than the dietary requirement (0.9 mg Cu/day, corresponding to ~0.013 mg Cu/kg body weight/day for a 70-kg human). 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 associated with Wilson's disease: accumulation of copper in the liver, decreased serum copper and ceruloplasmin levels, and impaired biliary excretion of copper (Sugawara et al. 1991, 1992, 1994; Suzuki et al. 1995).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to copper are discussed in Section 5.7, Populations with Potentially High Exposures.

Wilson's disease, an autosomal recessive disorder that causes liver dysfunction, typically has a childhood onset. Affected individuals can develop toxic tissue accumulations of copper, even with low levels of dietary exposure (reviewed by Taylor et al. 2020). They require lifelong medical treatment combined with a low-copper diet. Without medical treatment, Wilson's disease is fatal, usually early in life.

Another copper-related genetic disorder, ICT, is largely believed to be caused by an autosomal recessive genetic susceptibility causing excess copper accumulation and subsequent liver damage; however, it is unclear whether exposure to excess copper plays a role in disease manifestation or if it merely exacerbates symptoms (Müller et al. 1998; Nayak and Chitale 2013). Another disorder, ICC, is characterized by severe liver damage in infants and children (<5 years of age). It is suspected to be caused by a genetic predisposition due to its random occurrence in siblings and higher liver disease mortality in second-line family members (Nayak and Chitale 2013; Pandit and Bhave 1996). However, data are inconclusive on whether ICC is caused by external exposure to copper, such as the consumption of milk stored in copper or brass vessels, or endogenously through copper dysregulation in the body (Nayak and Chitale 2013; Tanner 1998). ICC was previously considered endemic to India, but it has been documented in children of non-Indian origin in other countries (Nayak and Chitale 2013). ICT and ICC lead to a loss of copper homeostasis in diagnosed children and may make them more susceptible to excess copper accumulation

especially early in life. In early stages of postnatal development, the mechanisms of copper intestinal absorption and excretion through bile are not fully developed causing children to be susceptible to even small excesses of copper in water (Puchkova et al. 2018).

Gastrointestinal upset, the most commonly reported adverse health effect in adults, has also been reported in infants and children. It is manifested as 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, no reliable information on copper concentration or dose was reported (Gill and Bhagat 1999; Karlsson and Noren 1965; Knobeloch et al. 1994; Spitalny et al. 1984; Walsh et al. 1977). 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 categorized as having gastrointestinal upsets, were described as “unusually irritable” or had recurrent headaches. In a second survey, mothers were asked to recall the frequency of gastrointestinal effects for all family members (Knobeloch et al. 1994). A significantly higher percentage of children, as compared to adults, were reported to have gastrointestinal effects. Recall bias can be affected by self-reporting or adult reporting of symptoms in children in the household. The available data are inadequate to assess accurately whether there is an age-related difference in the gastrointestinal toxicity of copper.

Copper accumulation in fetal tissues primarily occurs in the second half of pregnancy (Chernenkov et al. 2018). Approximately half of the copper in the fetus is stored in the liver, mostly bound to metallothionein. During that phase of a pregnancy, the rate of transfer of copper from the liver to the bile or blood is decreased due to the immaturity of the fetal liver. The magnitude of the amount of copper in the fetal liver is similar to levels observed in Wilson’s disease; however, the fetal and neonatal liver can tolerate these high concentrations (Olivares et al. 2000). Copper levels are imbalanced in early stages of postnatal development for all infants, as the mechanisms for excreting copper through bile and controlling copper absorption in the small intestine have not developed fully (Puchkova et al. 2018). After birth, copper levels decrease to normal levels in infants lacking a genetic defect (Chernenkov et al. 2018; Olivares et al. 2000).

Copper, likely bound to albumin, is found in human breastmilk and is necessary for infant development.

Copper was measured in breastmilk at concentrations of 0.12–0.69 mg/L (Choi et al. 2016; Domellof et al. 2004; Khaghani et al. 2010; Yalcin et al. 2015). Maternal dietary copper intake is not likely to affect copper concentrations in breastmilk (Choi et al. 2016); thus, excess dietary maternal copper intake may not impact infant copper intake from breastmilk. A study in lactating rats suggested that transport of copper to the mammary gland is about 60% following intraperitoneal or intravenous injection of ionic copper (Donley et al. 2002). Subsequently, the labeled isotopes rapidly appeared in milk and milk ceruloplasmin. These results were not found in nonpregnant rats, where transport was primarily to the liver and kidney.

The potential age-related differences in the toxicity of copper have been assessed in rats exposed to 120 mg Cu/kg/day as copper sulfate in the diet for 12 weeks (Fuentealba et al. 2000). The observed liver effects of enzyme activity alterations and hepatitis 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. Copper levels in the liver of young rats, 1,553–1,635 μg/g, were higher than in adult rats, 472–534 μg/g. It is uncertain if these data in rats would be suggestive of sensitivity in human infants and children.

Several studies investigated the potential developmental toxicity of excess dietary copper sulfate and copper hydroxide. Some results suggest that *in utero* exposure to copper can result in delays in growth and development in the offspring of mice (Lecyk 1980). However, some studies testing similar or lower doses in mice and mink observed no developmental effects in offspring (Aulerich et al. 1982; Kadammattil et al. 2018).

Some health conditions may influence sensitivity to the gastrointestinal effects of oral exposure to copper. For example, health conditions that reduce the pH of gastric secretions (e.g., acute *Heliobacter pylori* infection, some neuroendocrine tumors or gastrinomas, rebound acid hypersecretion after stopping proton pump inhibitor therapy) may result in higher concentrations of free copper ions in contact with the gastrointestinal tract than those seen in healthy individuals at the same dose. In addition, health conditions that result in damage to the integrity of the gastrointestinal tract (ulcers, acid reflux) may also increase a person's sensitivity to oral copper exposure.

A number of populations were identified as unusually susceptible to copper toxicity due to genetic defects that impair copper homeostatic mechanisms. Wilson's disease, also referred to as hepatolenticular degeneration, is an autosomal recessive disorder with an estimated prevalence of 1 case per 30,000 live

births among most populations (Schilsky 2019). The primary genetic defect in Wilson's disease is in the ATP7B gene that 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. The progression of the disorder begins with an accumulation of copper in the liver, structural damage to the liver, and subclinical liver cirrhosis (Rodriguez-Castro et al. 2015). Over time, the individual will develop hepatic, neurological, and psychiatric symptoms. The hepatic effects are characterized by jaundice, hypoalbuminemia, ascites, coagulation defects, hyperammonemia, hepatic encephalopathy, and/or liver failure. In the cases with massive liver failure, large amounts of copper are released from the liver, impacting red blood cells and leading to hemolytic anemia. Neurological symptoms include tremors, other movement disorders, and speech abnormalities. Psychiatric and behavioral symptoms are often found in individuals who also manifest 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 present in some individuals with Wilson's disease. Individuals who are heterozygotes for Wilson's disease may also be more susceptible to the toxicity of copper. Increases in urinary copper and hepatic concentrations and decreased copper incorporation into ceruloplasmin have been observed in heterozygotes. These findings suggest that long-term exposure to elevated levels of copper could result in copper overload.

Individuals with a common deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) could be more susceptible to the toxic effects of oxidative stressors such as copper (Calabrese and Moore 1979; Chugh and Sakhuja 1979; Sansinanea et al. 1996). Red blood cell models were used to analyze the effects of copper chloride on oxidative markers while measuring G6PD activity (Swastika et al. 2020). There was a negative correlation between G6PD activity and copper chloride dose. In the blood, most of the copper is bound to ceruloplasmin. With the exception of ingestion of a very large dose of a copper salt, the levels of non-ceruloplasmin-bound copper remain low. Thus, it is unlikely that this relatively small change in free copper would alter the survival of glucose-6-phosphate dehydrogenase deficient red blood cells.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for copper from this report are discussed in Section 5.6, General Population Exposure.

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 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to copper are discussed in Section 3.3.1.

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 2006). 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 effect caused by copper are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Copper levels can be readily measured in tissues, body fluids, and excreta. Depending on the dose and exposure duration, inhalation and/or oral exposure to copper can result in increased levels of copper in serum, urine, hair, and nails.

The normal serum copper level in human adults is 10–25 μmol/L (64–160 μg/dL) (IOM 2006). Serum copper levels can be used to evaluate copper toxicity, deficiency, or the possibility of copper metabolism disorders. Increased serum copper levels (>25 μmol/L) were reported in several human case studies following intentional ingestion of copper compounds, such as copper sulfate biocides (Chuttani et al. 1965; Franchitto et al. 2018; Yang et al. 2004). Serum copper levels reported in these studies ranged from 37 to 140 μmol/L. Elevated plasma copper was also measured in a 23-month-old child who had accidentally ingested an unknown amount of a disinfectant agent containing an unknown concentration of copper sulfate (Mortazavi and Jafari-Javid 2009). Fifteen days after admission, the patient's plasma copper level was 216 μg/dL (33.9 μmol/L) (normal range in 6-month-old to 6-year-old children: 14–30 μg/dL). Whole-blood copper levels measured in humans following intentional ingestion of copper sulfate ranged from 60.3 to 107.6 μmol/L, while in non-exposed individuals, the whole-blood copper was 34.1 μmol/L (Chuttani et al. 1965). Following chronic-duration inhalation exposure to 111–464 mg Cu/m^3 copper in dust, serum copper levels >31.8 μmol/L were observed in 16% of exposed factory workers (Suciu et al. 1981). However, increased serum copper levels may only be reflective of recent exposure. Chuttani et al. (1965) observed that serum ionic copper rapidly diminished within a few days to normal levels following ingestion of an acute bolus dose. Mortazavi and Jafari-Javid (2009) observed that in a 23-month-old child, copper levels took about 2 months to fall to within normal range, even after treatment with a chelating agent. A relationship between blood copper levels and the severity of symptoms has not been established. Among individuals intentionally ingesting a single dose of copper sulfate (1–30 g), there did not appear to be a correlation between serum copper levels and symptom severity (Chuttani et al. 1965). In contrast, whole-blood copper levels did have a significant relationship with the severity of symptoms.

Serum ceruloplasmin, a copper-related carrier protein, is a biomarker for copper exposure. Based on a significant correlation of serum copper with serum ceruloplasmin levels, it has been suggested that serum ceruloplasmin is a reliable biomarker for chronic-duration occupational exposure to copper (Saha et al. 2008). A human dietary study by Turnlund et al. (2004) reported that a high copper intake resulted in an increase of ceruloplasmin in subjects given supplements, when compared to controls. Nine men had been

exposed to 0.02 and 0.1 mg Cu/kg/day during separate 18-day period in a metabolic research unit (Turnlund et al. 2004). A metabolism study in rats observed increases in ceruloplasmin with copper exposure, as over 90% of the copper dose was found primarily in ceruloplasmin as opposed to other serum proteins (Weiss and Linder 1985).

Similar to serum, copper can be measured in urine, but this is primarily used to test for diseases affecting copper homeostasis and the liver. In one patient who intentionally ingested a copper sulfate containing fungicide, the urine copper level 3 days after admission was 112 µg/dL and decreased to 16 µg/dL in follow-up 11 days after admission (Yang et al. 2004).

Copper levels in hair and nails can also be used to assess copper exposure; however, the reliability of these biomarkers has not been established. 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 µg/g (range of 5.4–20.7 µg/g) and 7.5 µg/g (range of 3.0–18.6 µg/g), respectively. A study by Hopps (1977) calculated that for 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. In an occupational study of workers exposed to unspecified levels of copper from fossil fuel combustion, oil distribution workers had a mean hair copper level of 69.6 µg/g, which was significantly higher than in controls (defined in the study as non-exposed "healthy individuals living far from hazardous exposure with age and weight matching the test group") who had a mean hair copper level of 36.8 µg/g (Jaccob 2020). The study author suggested that hair levels may be a useful biomarker for copper and heavy metal exposure. Increased hair copper levels have been reported in workers exposed to 0.64–1.05 mg Cu/m^3 of an unspecified copper compound; the concentration of copper in their hair was 705.7 µg Cu/g, as compared to a concentration of 8.9 µg Cu/g in non-exposed workers (Finelli et al. 1981).

Based on a toenail growth rate of 1 mm/month, toenail samples would represent copper intakes over 12–18 months (Fleckman 1985). Increased hair and fingernail copper levels were observed in children with ICC (Sharda and Bhandari 1984). An epidemiological study found that mean toenail copper concentrations were significantly higher among residents who lived in copper-mining towns than those who did not (Ndilila et al. 2014). Among adults in the copper-mining town, the mean copper concentration in toenails was 132 mg/kg. The study authors suggested that copper levels in toenails may be an indicator of exposure.

3.3.2 Biomarkers of Effect

No copper-specific biomarkers of effects resulting from copper toxicity have yet been identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Numerous studies demonstrate the interaction between copper and metals such as cadmium, iron, and tin. Dietary zinc strongly affects copper absorption, and a diet high in zinc can result in copper deficiency by upregulating metallothionein, which binds to copper in enterocytes and decreases its absorption into plasma (Igic et al. 2002; Myint et al. 2018). Uptake of copper from the small intestine is susceptible to competition from other transition metals including zinc. Increased dietary zinc results in induction of metallothionein synthesis in the intestine. Since metallothionein has a greater binding capacity for copper than for zinc, dietary copper is sequestered in the intestinal mucosal cell metallothionein 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 both decreased copper absorption and decreased serum levels, it is considered an effective therapy for Wilson's disease (Ranucci et al. 2014).

Animal studies demonstrate that ingestion of copper and zinc ions simultaneously results in reduction of systemic copper toxicity because it decreases systemic uptake (Kheirandish et al. 2014). Mice given both zinc sulfate and copper sulfate had less histological damage in the testis compared to mice give copper sulfate only (Kheirandish et al. 2014). Similar results were observed in rats, as improvements in sperm counts, viability, and motility were observed in rats given copper sulfate and zinc sulfate, while no such recovery was seen over the same time period of rats only given copper sulfate (Babaei and Abshenas 2013).

A study in rats found that exposure to sodium arsenate resulted in increased copper concentration in the kidney (Cui and Okayasu 2008). Rats were orally exposed to varying doses of sodium arsenate daily for 4 and 16 weeks. Exposure to manganese in rats also increased copper uptake as demonstrated when a 7-day exposure to manganese in diet, water, or gavage resulted in increased copper levels in the liver (Mercadante et al. 2016). Exposure to manganese by diet and gavage resulted in decreased copper levels in bile; both effects suggest a relationship between manganese and copper hepatobiliary excretion. Several other divalent cations compete with copper for intestinal absorption. Exposure to dietary cadmium (Evans et al. 1970), iron (Ha et al. 2016), and stannous tin (Pekelharing et al. 1994; Wapnir et al. 1993) can result in decreased copper absorption. In the case of cadmium, the copper ion decrease is

related to cadmium's induction of metallothionein synthesis and the binding of copper to it. Tetrathiomolybdate is used for the treatment of Wilson's disease (Brewer et al. 2006); thus, excessive dietary molybdenum can also result in decreased copper uptakes and, therefore, alterations in copper utilization and toxicity. Two mechanisms of action of tetrathiomolybdate have been proposed: (1) it reacts with copper-metallothionein to form a soluble complex that is excreted (Ogra et al. 1996), and (2) it can complex with non-ceruloplasmin-bound plasma copper, impeding its cellular absorption (Brewer et al. 2006). Interactions with copper sulfate may differ, as molybdenum may lower the activity of sulfide oxidase, resulting in the accumulation of copper sulfide (Vyskocil and Viau 1999).

Vitamin C, also known as ascorbic acid, interferes with intestinal copper absorption resulting in reduced copper concentration in various tissue (Van Den Berg and Beynen 1992). This suggests that a diet high in vitamin C can result in copper deficiency.

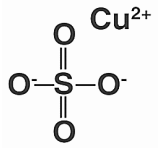
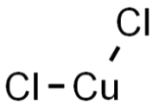
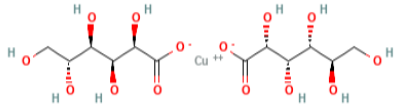
Several other natural substances have been tested in animals, and studies suggest that they may protect against copper toxicity. In mice, copper-induced toxicity changes in the liver, kidneys, and stomach were less pronounced in mice treated with copper sulfate and coriander, or copper sulfate, coriander, and zinc, compared to mice treated only with copper sulfate (Hashimyousif et al. 2019). Curcumin, the main active ingredient in turmeric and a natural anti-inflammatory agent, appeared to alleviate the hepatic and renal toxicity of copper sulfate (Hashish and Elgaml 2016). This was based on a comparison of hepatic enzyme levels, and liver and kidney antioxidant levels, between rats orally exposed to copper sulfate only and rats exposed to copper sulfate and curcumin at the same time or in succession. Resveratrol, an antioxidative compound, was observed to possibly attenuate copper sulfate-induced liver injury by decreasing oxidative stress and the concentrations of liver transaminases (Tian et al. 2019). An *in vivo* genotoxicity study using mouse blood cells reported that orange juice appeared to have a modulating effect on the action of metallic sulfate salts and was both restorative and protective of the copper-induced genotoxic effects (Franke et al. 2006). The study authors hypothesized that the genotoxic effects could be mediated by the interaction of unspecified orange juice components or that the juice's antioxidant byproducts can interact with transition metals.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Copper, atomic number 29 on the periodic table, is a transition metal and a Group 11 essential element that can occur naturally in elemental form. Copper exists in four oxidation states: Cu(0), Cu(I), Cu(II), and Cu(III). The most common oxidation states are cupric Cu(I), with a +1 oxidation state, and cuprous Cu(II), with a +2 oxidation state (Conry 2006). Both types can form stable complex ions (i.e., salts). Cu(II) is classified as a borderline hard acid and can form complexes with hard ligands such as nitrogen- and oxygen-donating ligands as well as chloride- and sulfur-containing species; Cu(I) is considered a soft acid and typically forms salt complexes with softer ligands (Conry 2006). In physiological systems, Cu(II) is reduced to Cu(I) for transport across cellular membranes (Nishito and Kambe 2018). Copper industrial uses include electrical products and equipment, wiring, piping, sheet metal, building material, machinery, and motors. Copper is found in many foods and in some dietary supplements. Copper is essential to human health and among the most abundant trace elements in the human body. Because copper exhibits various oxidation states and can form numerous stable salts, there are many forms of copper. Copper sulfate ($CuSO_4$) is an inorganic compound that can occur in nature. It is the most common compound used in commercial applications. It is the most widely used copper salt and is an ingredient in pesticide formulations, and has been used as a micronutrient additive for fertilizer and animal feed (NLM 2024). Copper chloride is another important copper salt. It is used as a catalyst in chemical reactions; in dyeing and printing; and in fungicides, wood preservative, feed additives, and water purification (Budavari et al. 2001; NLM 2024). Copper oxide is used in some paints, glasses, porcelain glazes, and ceramics as a red pigment, and has been used as a fungicide (Conry 2006). Copper nanoparticles are formed through natural processes or can be manmade. They are primarily used as antimicrobial, antibacterial, and antifungal agents. A summary of copper nanoparticle toxicity is in Section 2.21. Information regarding the chemical identity of copper and copper compounds is presented in Table 4-1.

Table 4-1. Chemical Identity of Copper and Copper Compounds

Characteristic	Information		
Chemical Name	Copper	Copper sulfate	Copper chloride
Synonym(s) and Registered trade name(s)	M1; M2; M3; M4; Cuprum; Gold Bronze; 1721 Gold; Bronze powder; Cobre; Cuivre; Rame; Allbri Natural Copper; M3R; M3S; E 115; OFHC CU	Cupric sulfate; Copper (II) sulfate; cupric sulfate anhydrous; copper sulphate; Blue stone; copper monosulfate; Hylinec; Trinagle; Delcup, cupric sulphate; sulfuric acid copper (2+) salt (1:1); monocopper sulfate	Copper(II) chloride; cupric chloride; cupric chloride anhydrous; cupric chloride dihydrate
Chemical formula	Cu	$CuSO_4$	$CuCl_2$
SMILES	Cu	[O-]S(=O)(=O)[O-].[Cu+2]	Cl[Cu]Cl
Chemical structure	Cu		
CAS Registry Number	7440-50-8	7758-98-7	7447-39-4
Chemical Name	Copper (II) oxide	Copper gluconate	
Synonym(s) and Registered trade name(s)	Cupric oxide; copper oxide; copper monoxide; CuO; oxocopper	Copper(II) gluconate; copper di-D-gluconate; copper (II) D-gluconate; copper(2+) D-gluconate, (1:2)	
Chemical formula	CuO	$C_{12}H_{22}CuO_{14}$	
SMILES	[O-2].[Cu+2]	C(C(C(C(C(C(=O)[O-])O)O)O)O)O.C(C(C(C(C(C(=O)[O-])O)O)O)O)O.[Cu+2]	
Chemical structure	**Cu=O**		
CAS Registry Number	1317-38-0	527-09-3	

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

Source: NLM 2024

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Copper is a metallic solid that is malleable and has high thermal conductivity, high electrical conductivity, low corrosivity, and alloying ability. Its malleability is attributed to its relatively low number of electrons on its outer shell. The properties of copper typically vary with purity. Metallic copper is naturally a reddish color, and when exposed to oxygen in the air, it forms copper oxide, which is black (Haynes et al. 2015). As copper reacts with carbon dioxide in the air, copper carbonates, which are

usually green, form. Copper is positioned below hydrogen in the electromotive-force series (lower reactivity); therefore, it will not displace hydrogen ions in water, and thus has no single displacement interaction with water. It is soluble in dilute acid and in ammonia with the presence of an oxidizing agent. Copper will undergo galvanic corrosion when in contact with other metals. Copper sulfate is typically produced by treating hot copper with sulfuric acid. The resulting material is a white-green solid when anhydrous and blue crystals when hydrated ($CuSO_4.5H_2O$) (Haynes et al. 2015). Copper chloride is produced by reaction of metallic copper with chlorine. It is a yellow-brown powder in the anhydrous form. Information regarding physical and chemical properties of copper and copper compounds is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Copper and Copper Compounds

Property	Information		
Chemical name	Copper	Copper (II) sulfate	Copper (II) chloride
Molecular weight	63.55 g/mol	159.61 g/mol	134.45 g/mol
Color	Reddish, lustrous	White, off-white when dehydrated; blue crystals when hydrated	Yellow to brown
Physical state	Solid	Solid	Solid
Melting point	1,083°C	590°C	630°C
Boiling point	2,595°C	650°C	993°C
Density at 20°C/4°C	8.94	3.6	3.39
Odor	Odorless	Pleasant odor	Odorless
Odor threshold: Water Air	 No data No data	 No data No data	 No data No data
Taste threshold	No data	No data	No data
Solubility: Water Organic solvent(s)	 Insoluble Slightly soluble in dilute acid and ammonia water	 Soluble Soluble in methanol Insoluble in ethanol	 Soluble in acetone, ethanol
Partition coefficients: Log K_{ow} Log K_{oc}	 No data No data	 No data No data	 No data No data
Vapor pressure at 20°C	1 mm Hg at 1,628°C	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.		
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Copper and Copper Compounds

Property	Information	
Chemical name	Copper (II) oxide	Copper gluconate
Molecular weight	79.55 g/mol	453.84 g/mol
Color	Steel-grey to black solid; black to brownish-black amorphous or crystalline powder or granules	Light blue crystalline powder
Physical state	Solid	Solid
Melting point	1,326°C (decomposes)	155–157°C (D-form)
Boiling point	1,026°C (decomposes)	No data
Density at 20°C/4°C	6.315 at 14°C/4°C	No data
Odor	Odorless	Odorless
Odor threshold:		
Water	No data	No data
Air	No data	No data
Taste threshold	No data	No data
Solubility:		
Water	Insoluble	30 g/100 mL water at 25°C
Organic and inorganic solvent(s)	Soluble in acids, and ammonia and ammonium carbonate solutions; soluble in alkali cyanides	Slightly soluble in alcohol; practically insoluble in most organic solvents
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure at 20°C	1 mm Hg at 1,628°C	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.	
Explosive limits	No data	No data

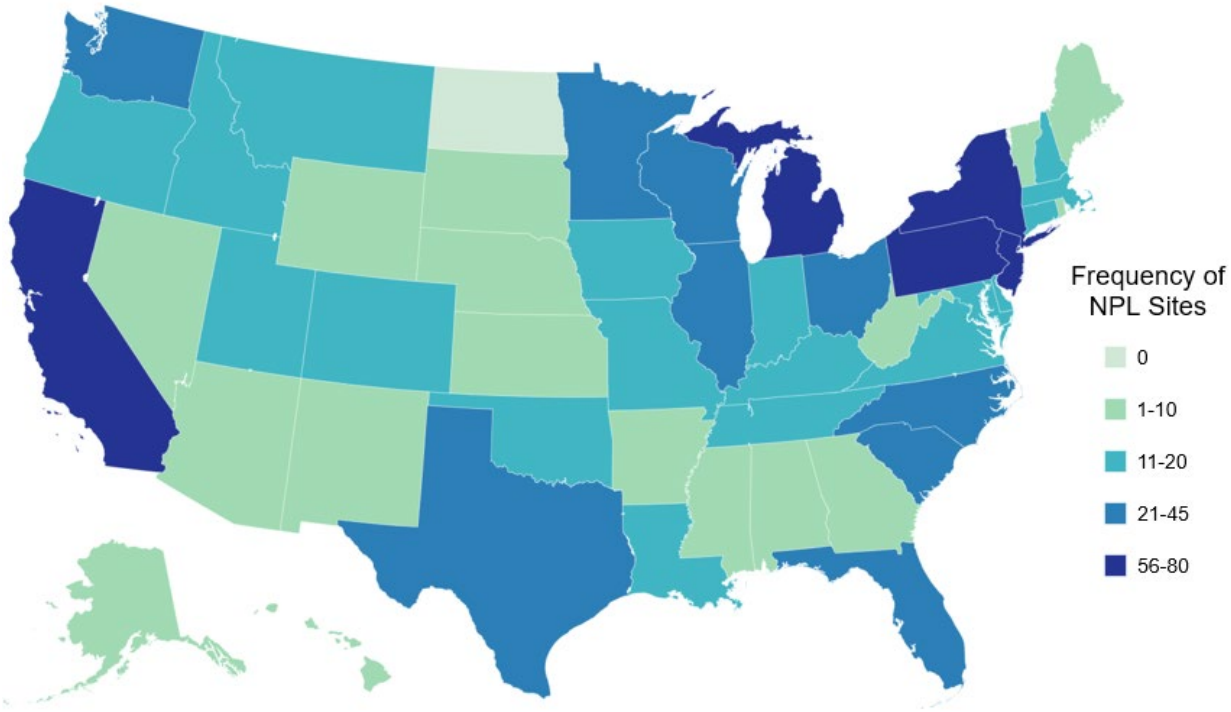
Sources: Haynes et al. 2015; NLM 2024

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Copper and copper compounds have been identified in at least 934 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites evaluated for copper and copper compounds is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 924 are located within the United States, 1 is located in Guam, 1 is located in the Virgin Islands, and 8 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Copper Contamination



Source: ATSDR 2022

- Copper occurs naturally both in many minerals and in the metallic state. The top 10 applications for copper in the United States, in order of percentage of total use, are building wire, plumbing, and heating, automotive, air conditioning, refrigeration and natural gas, power utilities, telecommunications, in-plant equipment, ordnance, business electronics, and lighting and wiring devices.

- Industrial effluents, mining, and production of copper and other metals, municipal solid waste management, and fossil fuel combustion account for a large portion of the total environmental releases of copper and copper compounds. Natural sources of copper releases include windblown dust, volcanoes, decaying vegetation, forest fires, and sea spray.

- Copper is an essential micronutrient present in many foods. Copper gluconate and copper sulfate are direct food additives generally recognized as safe by the U.S. Food and Drug Administration (FDA).

- The general population is expected to be exposed to copper daily via inhalation of ambient air, ingestion of foods and drinking water, and to a lesser extent dermally to materials containing copper.

- People living near copper smelters and refineries and workers in these and other industries may be exposed to high levels of dust-borne copper by both inhalation and ingestion.

Copper and its compounds are naturally present in the Earth's crust and can be discharged naturally to air and water during weathering. Mean copper concentrations in the atmosphere were 0.0182–0.0238 μg/m^3 at 13 U.S. locations from 2020 to 2021 (EPA 2022a). For 10 U.S locations reporting data for 2022, the mean value was 0.021 μg/m^3 and the maximum value was 0.0640 μg/m^3 (EPA 2022a). Airborne copper is associated with particulates that are derived from suspended soils, combustion sources, the manufacture or processing of copper-containing materials, and mine tailings. Copper associated with particulate matter is emitted into the air naturally from windblown dust, volcanoes, and anthropogenic sources, the largest of which are primary copper smelters and ore processing facilities. The major sources of releases to water are mining operations, agriculture, sludge from publicly owned treatment works (POTWs), and municipal and industrial solid waste. Mining and milling contribute the most waste. Copper is released to water because of natural weathering of soil and discharges from industries and sewage treatment plants. Copper compounds may also be intentionally applied to water as an aquatic herbicide to kill algae. Copper concentrations in groundwater vary widely from 0.2 to 98.4 μg/L (USGS 2020b). Copper is predominantly found in the Cu(II) ($^+$2 oxidation) state under environmental conditions, and most of it is complexed or tightly bound to organic matter. A small amount of copper is present as the free (hydrated) or readily exchangeable form. The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II) in the environment. 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. The USGS reported the median level of copper in soil and sediment as 30 ppm (USGS 2016). Copper concentrations will be higher in soils that are close to sources of copper emissions and mining activities.

In the general population, the highest exposures to copper come from the ingestion of drinking water and foods. Copper is found in organ meats, shellfish, and nuts, as well as some whole grains, chocolate, and leafy vegetables like spinach (see Section 5.5.4 and Table 5-22). Copper can leach into drinking water from contact surfaces within water distribution systems, water treatment plants, and in-home plumbing

systems. When a system has not been flushed after a period of disuse, the concentration of copper in tap water can exceed 1.3 mg/L, the EPA drinking water action level. Copper-contaminated water may have a light blue or blue-green color with a metallic, bitter taste (WHO 2004).

Many workers are exposed to copper in agriculture, industries connected with copper production, metal plating, and other industries. Based on the available data, people living close to NPL sites contaminated with copper may be at greater risk for exposure to copper than the general population with respect to inhalation of airborne particulates from the NPL sites, ingestion of contaminated water or soil, and/or uptake of copper by 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 dust-borne copper by both inhalation and ingestion routes.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Copper occurs naturally in many minerals, such as cuprite (Cu_2O), tenorite (CuO), malachite ($CuCO_3 \cdot Cu(OH)_2$), azurite ($2CuCO_3 \cdot Cu(OH)_2$), antlerite ($CuSO_4 \cdot 2Cu(OH)_2$), brochantite ($CuSO_4 \cdot 3Cu(OH)_2$), chrysocolla ($CuO \cdot SiO_2 \cdot 2H_2O$), chalcopyrite ($CuFeS_2$), chalcocite ($Cu_2S$), covellite (CuS), and bornite (Cu_5FeS_4). It also occurs as copper metal (Davenport 2001). Copper is most commonly present as copper-iron-sulfide and copper sulfide minerals (Schlesinger et al. 2011a). The copper content of ores ranges from 0.5 to 1 or 2% copper (Schlesinger et al. 2011a). Most copper is obtained from copper-iron-sulfur ores, such as chalcopyrite and chalcocite, and the principal copper ore mineral is chalcopyrite, which yields a matter of approximately 50% copper (Morris and Wadsley 2001; Schlesinger et al. 2011a). The most common process to produce copper is via pyrometallurgical technology, accounting for about 80% of global processes; production of pure copper metal typically involves concentrating, smelting, and electrolytic refining of low-grade ores containing copper-sulfide minerals (Adrianto et al. 2022; Haynes et al. 2015; USGS 2022).

Domestic mine production of recoverable copper in the United States totaled 1.3 million tons in 2019, 1.2 million tons in 2020, and 1.23 million tons in 2021 (USGS 2022). The average daily mine production in January of 2022 increased by 14% compared to production in January 2021. In 2015, the recoverable copper content per unit of ore mined was 0.47% (USGS 2017b). The United States is the world's fourth leading copper producer, along with Congo and following Chile, China, and Peru (USGS 2020a). Based

on data from S&P Global Market Intelligence, annual global production of copper in 2019 equaled 20.5 Mt (Adrianto et al. 2022). In 2021, copper was actively mined in seven states with Arizona accounting for 71% of U.S. copper production, and active operations in Utah, New Mexico, Nevada, Montana, Michigan, and Missouri (USGS 2020a). There were 25 copper-producing U.S. mines in 2021, with 19 mines accounting for 99% of production in the United States.

Tables 5-1 and 5-2 summarize information on companies that reported the production, import, or use of copper and copper compounds, respectively, for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	3	1,000	99,999	12
AL	72	0	999,999,999	1, 5, 7, 8, 9, 10, 11, 12, 13, 14
AR	46	0	49,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12, 14
AZ	24	0	9,999,999	1, 4, 5, 7, 8, 11, 12, 13
CA	94	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
CO	9	0	999,999	2, 3, 4, 8, 11, 12, 14
CT	40	1,000	9,999,999	2, 3, 4, 8, 9, 12, 14
DE	2	1,000	9,999	7, 8, 11
FL	33	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	61	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14
HI	3	0	999,999	9, 12
IA	50	1,000	9,999,999	1, 2, 3, 5, 7, 8, 9, 11, 12, 14
ID	10	0	999,999	1, 8, 9, 11, 12, 13, 14
IL	122	0	99,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
IN	132	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
KS	43	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
KY	55	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	19	0	9,999,999	1, 2, 5, 7, 8, 9, 10, 12, 13, 14
MA	44	1,000	9,999,999	1, 3, 6, 7, 8, 9, 11, 12, 14
MD	5	1,000	999,999	2, 3, 4, 8, 12
ME	8	1,000	999,999	7, 8, 9, 12
MI	117	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	54	0	9,999,999	2, 3, 7, 8, 11, 12, 13, 14
MO	66	0	9,999,999	1, 5, 7, 8, 9, 11, 12, 14
MS	31	1,000	49,999,999	2, 3, 7, 8, 12

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MT	1	1,000	9,999	1, 5, 12
NC	79	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
ND	3	1,000	99,999	8
NE	17	10,000	9,999,999	7, 8, 11, 14
NH	17	100	9,999,999	2, 3, 7, 8, 9, 11, 12
NJ	29	100	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12
NM	3	10,000	99,999	8, 12
NV	13	1,000	9,999,999	1, 2, 3, 4, 5, 8, 9, 11, 12
NY	79	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 14
OH	185	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	58	100	499,999,999	6, 7, 8, 9, 11, 12, 14
OR	12	0	999,999	1, 5, 7, 8, 12, 14
PA	198	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
PR	10	100	9,999,999	7, 8, 9, 11
RI	16	1,000	9,999,999	1, 3, 4, 7, 8, 9, 12, 14
SC	64	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
SD	13	1,000	999,999	1, 5, 7, 8, 14
TN	72	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
TX	118	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14
UT	13	1,000	9,999,999	2, 3, 7, 8, 12
VA	36	0	9,999,999	7, 8, 11, 12, 14
VT	4	1,000	99,999	2, 3, 8, 9, 11, 12
WA	20	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 14
WI	149	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
WV	5	10,000	9,999,999	2, 3, 7, 8
WY	3	100	99,999	1, 2, 4, 9, 12, 13

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

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

Source: TRI22 2024 (Data are from 2022)

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	7	1,000	9,999,999	1, 5, 6, 8, 10, 12, 13, 14
AL	57	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	48	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	27	100	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	67	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CO	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CT	17	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
DC	1	10,000	99,999	12
DE	6	10,000	99,999	8
FL	42	100	9,999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	61	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IA	37	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	16	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IL	75	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	63	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	13	100	999,999	1, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14
KY	40	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	30	0	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MA	8	1,000	999,999	1, 2, 4, 5, 7, 8, 11, 14
MD	14	100	9,999,999	1, 3, 4, 5, 7, 8, 9, 12, 13
ME	3	100	999,999	1, 5, 7, 14
MI	59	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	40	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MO	52	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MS	28	1,000	49,999,999	1, 2, 3, 4, 5, 8, 10, 13, 14
MT	9	100	49,999,999	1, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14
NC	61	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
ND	6	1,000	999,999	1, 3, 5, 10, 12, 13, 14
NE	22	100	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	7	1,000	999,999	1, 3, 5, 6, 8, 9, 11, 14
NJ	12	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 14
NM	7	1,000	49,999,999	1, 3, 4, 5, 8, 9, 11, 12, 13, 14
NV	16	0	49,999,999	1, 4, 5, 10, 12, 13, 14
NY	22	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 14
OH	76	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	22	0	999,999	1, 2, 3, 4, 5, 8, 9, 10, 12, 13, 14
OR	23	0	9,999,999	1, 2, 3, 5, 6, 8, 10, 11, 12, 14
PA	82	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	8	10,000	9,999,999	1, 5, 8, 12, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
RI	7	1,000	999,999	7, 8, 11, 12, 14
SC	34	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	8	0	0	0
TN	54	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
TX	119	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	19	1,000	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
VA	32	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
VI	1	10,000	99,999	10
VT	2	0	0	0
WA	19	100	49,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	48	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
WV	18	1,000	999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
WY	6	0	999,999	1, 2, 3, 4, 5, 12, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

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

Source: TRI22 2024 (Data are from 2022)

Copper from oxidized minerals is usually produced by leaching, solvent extraction, and electrowinning (Schlesinger et al. 2011b). Since most copper comes from Cu-Fe-S ores that are not easily dissolved by aqueous solutions, most extraction occurs by concentration, smelting, and refining (Schlesinger et al. 2011b). This extraction occurs by crushing and grinding the ore and then isolating mineral particles to a concentrate by froth flotation, smelting the concentrate to a matte, oxidizing the matte to impure molten copper, and then fire- and electrorefining the copper (Schlesinger et al. 2011b).

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. There are three types of scrap: home scrap (copper that primary producers cannot further process or sell), old scrap (metal that has been used in products), and new scrap (generated during manufacturing) (Schlesinger et al. 2011c). In 2015, smelting was performed in the United States by three smelters, with a combined production of 527,000 metric tons per year (USGS 2017b). During 2015, three refineries produced

1,090,000 metric tons of copper from primary sources and 48,800 from secondary materials (scrap), for a combined total refinery production in the United States of 1,140,000 tons (USGS 2017b). Production of secondary copper amounted to 805,000 metric tons in 2015 (USGS 2017b). In 2019, 3 smelters, 3 electrolytic refineries, 4 fire refineries, and 14 electrowinning facilities operated in the United States (USGS 2020a). Refineries produced 1,000,000 metric tons from ore and 45,000 metric tons from scrap, for a total refinery production of 1,045,000 metric tons.

Copper sulfate is also produced as a byproduct of copper production by ore-leaching with sulfuric acid as the solvent. Production of copper sulfate in the United States increased from 22,800 metric tons in 2011 to 23,000 metric tons in 2013 but decreased to 18,497 metric tons in 2015 (USGS 2017b). Production figures for other copper compounds are not reported by the USGS.

5.2.2 Import/Export

In 2021, 13,000 metric tons of unmanufactured copper and 920,000 metric tons of refined copper were imported into the United States (USGS 2022). Chile, Canada, and Mexico were the principal sources of imported refined copper. Imports of copper sulfate amounted to 43,900 metric tons in 2015 and were primarily obtained from Mexico (USGS 2017b).

In 2021, the United States exported 360,000 metric tons of unmanufactured copper and 50,000 metric tons of refined copper (USGS 2022). In 2015, copper scrap was the leading U.S. copper export at 426,000 metric tons (USGS 2017b). Exports of copper sulfate amounted to 6,170 metric tons in 2015 (USGS 2017b).

5.2.3 Use

Copper is one of the most important metals used in industries because of its resistance to corrosion, antimicrobial properties, durability, ductility, malleability, and electrical and thermal conductivity. It is used primarily as copper metal or in alloys. Copper alloys, including brass and bronze, are important commodities (USGS 2009a). Currently, American coins are copper alloys (USDT 2018). A small percentage of copper production goes into the manufacture of copper compounds, primarily copper sulfate.

After accounting for production, imports, and exports, 1,800,000 metric tons of copper were available for use in 2019 (USGS 2020a). The Copper Development Association estimated that the end-use distribution of copper and copper alloy products in 2019 were: building construction, 43%; electrical and electrical products, 20%; transportation equipment, 20%; consumer and general products, 10%; and industrial machinery and equipment, 7% (USGS 2020a). The top 10 applications for copper in the United States, in order of percentage of total use, are building wire, plumbing and heating, automotive, air conditioning, refrigeration and natural gas, power utilities, telecommunications, in-plant equipment, ordnance, business electronics, and lighting and wiring devices (Schlesinger et al. 2011b). Copper plumbing is used in water distribution systems (Edwards et al. 2001; EPA 1995; Grace et al. 2012; Knobeloch et al. 1998; Lagos et al. 2001; Rajaratnam et al. 2002; Schock and Sandvig 2009; Turek et al. 2011). Copper and its salts are also used in cookware, kitchen utensils, and mugs; marine antifouling paints; animal feed supplements; fertilizers, fireworks; brake pads; water pipes; roofs; gutters; shingles; wood preservatives; and tires (Banavi et al. 2020; Koo et al. 2020; Lifset et al. 2012; Ni and Li 2008).

EPA has registered about 300 copper compounds and alloys as antimicrobial agents (Vincent et al. 2016). Copper-silver ionization filters have been used in hospital water systems to control waterborne pathogens (Huang et al. 2008; Rohr et al. 1999), and copper sulfate is used as an algaecide and bactericide in drinking water in the United States (NSF 2021). Since copper's antimicrobial properties make it useful for drinking water treatment and distribution, it also has potential uses for reducing microbial contamination and health care-associated infections by controlling microorganisms in heating ventilation and air-conditioning systems (Arendsen et al. 2019; Vincent et al. 2016). Aside from possible use for controlling contamination and infections, copper has some other uses in medicine and health care. Copper-containing ointments are used in anthroposophical medicine (Gorter et al. 2004). Copper IUDs are commonly used forms of birth control (Gu et al. 2012; Wildemeersch et al. 2014). Copper is also available in multivitamins, dietary supplements, and fortified foods.

Copper and copper compounds have many applications in agriculture, food processing, and production. Copper and copper compounds are registered as fungicides, bactericides, algaecides, herbicides, insecticides, and molluscicides for use on almost all food and feed crops (EPA 2009b). Copper can be present in growth stimulants and fertilizers for plants. Copper sulfate is used in land-applied pesticides in United States agriculture, primarily as a fungicide and bactericide for fruits and vegetables, and as an algaecide in reservoirs and waterways (Lifset et al. 2012). Industrial applications of copper sulfate include use as an activator in froth flotation of sulfide ores, production of chromated copper arsenate (CCA) wood preservatives, electroplating, azo dye manufacturing, mordant for textile dyes, petroleum

refining and in the manufacture of other copper salts such as copper hydroxide and copper carbonate (Mannsville Chemical Products 1984).

USGS estimates annual agricultural pesticide use in U.S. counties as part of the Pesticide National Synthesis Project. Estimated use for copper and copper compounds pesticides is presented in Table 5-3.

Table 5-3. Estimated Pesticide Use (kg) in the United States from 2013 to 2017

	Range				
Compound	2013	2014	2015	2016	2017
Copper	345,176–391,165	393,407–435,968	416,161–478,510	528,201–540,102	435,373–531,312
Copper hydroxide	2,218,149–2,378,077	1,867,194–1,951,160	1,952,598–2,129,077	1,989,599–2,101,067	2,063,632–2,204,163
Copper sulfate	924,911–1,017,101	1,014,369–1,077,501	969,716–1,026,607	931,604–958,736	1,135,793–1,270,874
Copper sulfate tribasic	465,364	456,608	601,444	603,385	638,114
Copper oxychloride	142,874–144,116	116,065–120,032	214,475–247,904	206,268–217,275	257,866–290,005
Copper oxychloride	50,723–136,649	67,750–114,027	67,025–107,164	61,052–100,496	10,535–16,516
Copper octanoate	4,439–4,463	7,730–7,938	10,056–10,179	11,184–11,230	12,117–12,448

Source: USGS 2017a

Copper is widely used in many applications, and demand is projected to increase. However, as ore grades and natural deposits are depleted, more emphasis may be put on a circular economy of copper and secondary production (Ciacci et al. 2020; Schipper et al. 2018). Under different models to explore the impacts of different futures on global copper supply/demand, demand is estimated to increase by 300–2,100% through 2100, depending on population, welfare, and renewable energy development (Schipper et al. 2018). All scenarios result in increased demand that would deplete copper resources (Schipper et al. 2018). While increasing secondary flows and recycling could meet increasing demands and result in a circular economy, most scenarios analyzed by Ciacci et al. (2020) for Europe would not meet greenhouse gas reduction targets unless green technology and equitable lifestyles are emphasized.

5.2.4 Disposal

Based on a review of several papers, it is estimated that 40–84% of copper in waste materials is recovered, depending on the country (Schlesinger et al. 2011c). The recycling rate in the United States is estimated to be between 29 and 49% (Lifset et al. 2002, 2012). In 2019–2021, copper in scrap was estimated to contribute about 32–35% of the U.S. copper supply (USGS 2020a, 2022). There are several recycling processes depending on the copper content of scrap material, other metals present in the scrap, and size. Clean, high-grade copper scrap can be re-melted and recovered without further refining, while scrap of lower grade must be refined, often through electrorefining (Samuelsson and Björkman 2014). Copper is removed from industrial wastewaters using a variety of processes, including chemical precipitation, ion exchange, membrane filtration, flotation, electrochemical treatment, coagulation/ flocculation, and adsorption (Bilal et al. 2013). Copper and copper compounds that are not recycled are disposed of in landfills (Cui and Zhang 2008).

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 (NLM 2024). 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 (NLM 2024).

Liquid spills containing copper should be cleaned up via adsorption using vermiculite, dry sand or earth, or a similar adsorbent. Copper dusts or mists and copper compounds can be disposed of in sealed containers in secure landfills (EPA 1986).

Disposal and use of sewage sludge containing heavy metals such as copper must be monitored in accordance with regulations found in EPA (1993).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI

chemical in excess of 10,000 pounds, in a calendar year (EPA 2022b). TRI releases of copper and copper compounds to the environment are provided in Tables 5-4 and 5-5, respectively.

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Copper[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	72	6,974	34,865	0	246,905	15,194	40,047	263,891	303,938
AK	2	0	240	0	34,077	0	34,077	240	34,316
AZ	24	18,238	314	0	25,123	45	43,305	416	43,720
AR	45	5,267	236	0	215,825	56,918	194,717	83,529	278,246
CA	92	1,310	408	0	1,148,918	27,124	1,124,544	53,216	1,177,760
CO	9	272	113	0	139,681	23,754	130,423	33,397	163,820
CT	40	66	168	0	1,075	261	95	1,476	1,571
DE	2	10	75	0	5	0	10	80	90
FL	33	102	34,355	36,877	111,892	44,892	148,495	79,624	228,118
GA	61	2,524	1,981	0	522,783	3,991	475,216	56,064	531,280
HI	3	2	0	0	86,237	0	86,239	0	86,239
ID	10	57	7	0	306,293	729	305,808	1,278	307,086
IL	122	11,424	20,972	924	375,595	6,494,632	55,382	6,848,165	6,903,547
IN	131	19,338	4,350	4,089	1,099,100	5,775,408	65,033	6,837,250	6,902,283
IA	50	4,337	722	0	39,330	2,766	5,056	42,099	47,155
KS	43	886	1,078	0	53,259	5	24,334	30,894	55,228
KY	55	38,376	387	0	246,046	5,736	173,495	117,052	290,547
LA	19	319	1,070	1,100	82,891	4	54,665	30,718	85,383
ME	8	8	36	0	1,552	5,738	12	7,321	7,333
MD	5	602	42	0	0	0	602	42	644
MA	44	1,005	1,440	0	22,491	15,418	1,011	39,344	40,354
MI	114	9,706	1,444	7,923	215,535	28,883	45,725	217,765	263,490
MN	54	5,430	134	0	75,711	46,097	64,095	63,277	127,373
MS	31	28,823	3,455	0	63,843	20,601	83,893	32,829	116,723
MO	66	3,856	459	0	265,391	16,740	236,029	50,417	286,446
MT	1	148	0	0	2,806	0	148	2,806	2,953
NE	17	1,456	36	0	527	1,720	1,456	2,283	3,739
NV	12	23	3	0	535,359	37	535,248	173	535,421
NH	17	38	131	0	85,413	22,582	137	108,027	108,164
NJ	29	9,609	135	0	79,805	202,408	35,820	256,137	291,957
NM	3	0	0	0	147,622	0	147,622	0	147,622
NY	79	2,181	22,775	0	123,771	16,915	112,172	53,470	165,642

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Copper[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
NC	77	5,088	21,546	0	566,974	9,955	518,777	84,786	603,563
ND	3	21	25	0	0	0	45	1	46
OH	185	24,056	1,232	206,314	336,353	76,751	302,273	342,433	644,706
OK	58	5,133	515	0	428,637	140	418,180	16,245	434,425
OR	12	360	20	0	82,463	3,024	82,821	3,046	85,867
PA	198	25,765	2,066	418	456,691	23,981	162,600	346,323	508,922
RI	16	234	42	0	821	5,845	239	6,702	6,941
SC	64	2,597	1,241	0	212,265	29,784	149,697	96,190	245,887
SD	13	5,055	42	0	460	24	5,249	332	5,581
TN	72	2,771	8,629	0	520,107	37,797	293,143	276,161	569,304
TX	118	6,510	1,419	19,349	312,848	87,179	299,856	127,448	427,304
UT	12	40	12	0	11,973	0	11,995	30	12,026
VT	4	0	1	0	17,786	4	17,381	410	17,791
VA	35	12,098	2,440	0	155,932	6,602	162,032	15,040	177,072
WA	20	1,340	1,228	0	154,992	244,565	149,510	252,615	402,125
WV	4	795	442	0	0	51	824	464	1,289
WI	148	4,486	932	0	162,047	60,354	54,839	172,980	227,819
WY	3	55	1	0	90,830	0	90,886	0	90,886
PR	10	22	46	0	10	576	22	632	654
Total	2,345	268,816	173,311	276,994	9,866,050	13,415,227	6,945,279	17,055,117	24,000,396

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

Table 5-5. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	57	1,919	4,345	0	3,133,832	11,189	2,966,114	185,172	3,151,286
AK	7	13,481	42	0	5,902,493	0	5,911,816	4,200	5,916,016
AZ	27	108,628	22,597	0	17,721,038	2,851	17,569,851	285,262	17,855,114
AR	48	2,088	1,461	0	599,036	39,743	558,819	83,509	642,328
CA	67	1,815	7,426	0	1,307,293	19,533	947,345	388,722	1,336,067
CO	21	5,042	46	0	231,332	0	196,158	40,262	236,421
CT	17	436	1,718	0	159,251	16,349	544	177,210	177,755
DE	6	0	0	0	0	213	0	213	213
DC	1	0	0	0	7,407	0	7,407	0	7,407
FL	42	939	7,002	0	142,139	29,874	71,193	108,761	179,954
GA	61	8,235	14,505	0	148,326	11,852	48,308	134,609	182,918
ID	16	502	412	0	702,605	10,569	480,604	233,483	714,088
IL	72	16,450	28,271	86	753,277	121,193	318,713	600,564	919,277
IN	62	30,931	15,096	484	845,960	199,021	569,785	521,708	1,091,492
IA	36	7,747	1,812	0	163,359	5	68,285	104,638	172,923
KS	13	646	296	28	95,205	11,133	95,701	11,607	107,309
KY	40	7,809	49,423	2	1,262,017	8,117	635,343	692,026	1,327,369
LA	30	8,458	2,925	25	1,415,050	13,197	1,258,466	181,189	1,439,654
ME	3	91	149	0	30,935	0	240	30,935	31,175
MD	14	14	4	0	23,649	3,600	18	27,249	27,267
MA	8	19	1,716	0	617	19,359	21	21,691	21,712
MI	58	6,502	20,099	0	1,603,420	16,102	1,367,108	279,015	1,646,123
MN	40	1,146	1,141	0	368,718	7,798	182,503	196,299	378,802
MS	28	4,918	386	23,938	178,557	11,222	69,600	149,421	219,021
MO	52	8,825	2,173	0	3,424,958	16,119	3,284,653	167,421	3,452,074
MT	9	13,674	10	0	18,808,090	0	18,746,910	74,864	18,821,774
NE	22	2,041	564	0	140,888	1,886	122,844	22,535	145,378
NV	13	2,590	0	260	5,165,860	1,692	5,168,099	2,303	5,170,402
NH	7	0	179	0	20	6,542	0	6,741	6,741
NJ	12	11,804	8,698	0	5,479	138,315	11,805	152,491	164,297
NM	7	4,318	1,059	0	162,753	23,658	167,840	23,948	191,788
NY	22	18,565	7,098	0	29,864	40,198	34,643	61,081	95,724
NC	61	11,793	1,218	0	201,412	21,770	195,683	40,509	236,192
ND	5	851	81	0	191,546	1,640	154,109	40,009	194,118
OH	76	8,357	30,474	0	956,021	175,820	451,193	719,479	1,170,672
OK	22	3,800	31	0	314,333	88	288,813	29,438	318,251

Table 5-5. Releases to the Environment from Facilities that Produce, Process, or Use Copper Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	23	8,729	13,532	0	423	8,859	9,195	22,347	31,543
PA	82	10,002	4,535	0	777,519	129,742	310,793	611,006	921,799
RI	7	28	8,214	0	0	25,130	128	33,245	33,373
SC	34	1,419	5,047	0	623,482	14,124	558,992	85,080	644,072
SD	8	0	0	0	0	0	0	0	0
TN	54	2,125	16,670	85,981	1,718,996	13,271	1,486,714	350,328	1,837,042
TX	118	28,739	38,040	98,966	992,879	142,800	929,651	371,774	1,301,424
UT	19	90,816	771	0	53,110,614	4,440	53,181,512	25,130	53,206,642
VT	2	0	0	0	0	0	0	0	0
VA	32	5,150	5,292	0	86,341	28,040	33,862	90,960	124,823
WA	19	6,929	496	0	23,696	332,659	8,429	355,350	363,779
WV	18	3,979	401	0	732,674	1,568	593,563	145,059	738,622
WI	48	2,473	7,923	1,274	208,843	7,431	40,023	187,922	227,944
WY	6	1,625	20	0	185,489	0	154,298	32,836	187,134
PR	8	1,326	57	0	36,382	0	1,383	36,382	37,765
VI	1	0	5	0	0	0	5	0	5
Total	1,561	477,776	333,462	211,044	124,694,079	1,688,708	119,259,083	8,145,986	127,405,069

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

Industrial releases such as industrial effluents, mining and production of copper and other metals, municipal solid waste management, and fossil fuel combustion account for a portion of the total environmental releases of copper and copper compounds. Other sources of copper released into the

environment include pesticides, marine paints, animal feeds, fertilizers, fireworks, brake pad wear, copper pipe corrosion, leaching from architectural surfaces, releases from treated wood, vehicle fluid leaks, tire wear, wood combustion, biomass burning, and sewage sludge (Lifset et al. 2012; Rauch and Graedel 2007). Natural sources of copper releases include windblown dust, volcanoes, decaying vegetation, forest fires, and sea spray (Georgopoulos et al. 2001; Rauch and Graedel 2007).

5.3.1 Air

Estimated releases of 268,816 pounds (~122 metric tons) of copper to the atmosphere from 2,345 domestic manufacturing and processing facilities in 2022, accounted for about 1.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 477,776 pounds (~217 metric tons) of copper compounds to the atmosphere from 1,561 domestic manufacturing and processing facilities in 2022, accounted for about 0.38% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-5.

Copper is emitted into the air from both natural and anthropogenic sources. Global atmospheric concentrations and releases of copper from manmade and natural sources have been estimated (Rauch and Graedel 2007). Estimates for the natural and anthropogenic emissions copper from various sources in the mid-1990s are shown in Tables 5-6 and 5-7. Based on these data, 6.9×10^7 kg/year of copper from natural sources is estimated to be emitted to the atmosphere.

Table 5-6. Global Emissions of Copper from Anthropogenic Sources in the mid-1990s

Source	Emissions (Gg[a] Cu/year)
Metal production	18
Nonferrous metal production	18
Iron and steel production	0.14
Fossil fuel combustion	7.1

Table 5-6. Global Emissions of Copper from Anthropogenic Sources in the mid-1990s

Source	Emissions (Gg[a] Cu/year)
Metal fabrication	1.4
Metal discard management	0.62

[a]One Gg is one billion (10^9) g. It is the same as one million (10^6) kg.

Source: Rauch and Graedel 2007

Table 5-7. World Total Copper Emissions into the Atmosphere in 1995

Source	Emissions (tonnes/year)
Primary copper production	17,708
Secondary copper production	160
Primary lead production	23
Secondary lead production	2
Primary non-ferrous metals production	17,909
Secondary non-ferrous metals production	162
Primary and secondary zinc production	177
Stationary fossil fuel combustion	7,081
Pig iron and steel production[a]	142
Municipal waste incineration[b]	547
Sewage sludge incineration[b]	74

[a]In 1994.
[b]In the mid-1990s.

Source: Pacyna and Pacyna 2001

Windblown dusts account for an estimated global emission of 5.0×10^7 kg/year of copper into the atmosphere (Rauch and Graedel 2007). Other natural sources of copper emitted into air (in order of highest to lowest worldwide emissions) are sea salt spray, biomass burning, and volcanoes. Anthropogenic emission sources include nonferrous metal production, fabrication, and use; fossil fuel combustion; metal production; and mining. Lifset et al. (2012) estimates the following emissions to the atmosphere in the United States: fireworks (2.2×10^5 kg/year), copper primary production (4.7×10^5 kg/year), copper waste management (1.9×10^5 kg/year), coal combustion (1.36×10^6 kg/year), oil combustion (4.5×10^5 kg/year), metals production (2.0×10^4 kg/year), and wood combustion (4.0×10^4 kg/year).

Daily stack emission rates have been reported for three coal-burning power plants on a kg/day/1,000-megawatt basis (Que Hee et al. 1982); they were 0.3–0.7 and 2.00 kg/day/1,000 megawatts for those using low-sulfur western coal and high-sulfur eastern coal, respectively. This amounted to annual emission rates of 110–260 kg/1,000 megawatts for the low-sulfur western coal and 730 kg/1,000 megawatts for the high-sulfur eastern coal.

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 most common control for reducing fugitive dust is the manual use of water sprays (EPA 1980a). The highest concentrations of copper in atmospheric particulate matter were obtained from mining activities, primary and secondary production, and industrial manufacturing (Table 5-8).

Table 5-8. Concentrations of Copper in Particulate Matter (<10 µm) Generated from Various Sources

Source[a]	Median
Metal mining	6.17[b]
Secondary metal production	4.60[b]
Primary metal production	3.50[b]
Industrial manufacturing	2.16[b]
Steel production	0.55[b]
Gray iron foundries	0.19[b]
Steel foundry, general	0.17[b]
Solid waste	0.09[b]
Food and agriculture	0.05[b]
Chemical manufacturing	0.03[b]
Petroleum industry	0.03[b]
Gasoline vehicle exhaust	0.05[c]
Paved road dust	0.0162[c]
Construction dust	0.0102[c]
Landfill dust	0.0102[c]
Unpaved road dust	0.0087[c]
Agricultural lands, dust	0.0067[c]
Diesel vehicle exhaust	0.003[c]

[a]Values obtained from CEIDARS 2000.
[b]Data obtained from EPA Speciate 3.0; Shareef, G.S; Radian, September 1987.
[c]Data obtained from KVB literature search.

Romo-Kröger et al. (1994) were able to show, through the use of radioactive tracers and cluster analysis of inter-elemental correlations, that copper, arsenic, sulfur, and zinc 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 to 22 ng/m^3 of fine particles and from 131 to 50 ng/m^3 of coarse particles during a period of inactivity at the plant, demonstrating the contribution of plant emissions to copper levels in the surrounding area.

Copper and other pollutants are present in fugitive dust originating from copper production sites or from waste sites. 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 suspended 1–3 m above the ground. The deposition rate was then determined from the amount of copper in the moss bags accumulated over the summer of 1985 and compared with that for an agricultural control area. The mean copper deposition rates in the two areas were about the same: 0.55 mg/kg-month (range 0.04–1.6 mg/kg-month) over the refuse dump and 0.51 mg/kg-month (range 0.26–0.76 mg/kg-month) in the control area (Lodenius and Braunschweiler 1986). Lodenius and Braunschweiler (1986) concluded that the refuse dump did not contribute to copper concentrations in urban air above normal values.

A study of automobile exhaust emitted from light-duty vehicles conducted in Denver, Colorado showed that this source of copper emission makes a small local contribution to copper in air. The amount of copper emitted in exhaust from automobiles powered by regular gasoline has been measured to be 0.001–0.003 mg/mile driven using the Urban Dynamometer Driving Schedule of the Federal Test Schedule during the summer of 1996 and the winter of 1997 (Cadle et al. 1999). Diesel-powered vehicles were also studied and found to emit 0.005–0.039 mg of copper per mile driven for vehicles using #2 diesel fuel.

Only in a few cases has the form of copper released into the air been determined. Copper released into the atmosphere can be in particulate matter in the elemental form or in the form of an oxide, sulfate, or carbonate, or other compound depending on the source material and conditions under which it is emitted. Because copper smelters co-emit sulfur oxides 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 oil-fired power plants and open-hearth steel mills (EPA 1980b). Copper associated with particles (≤10 μm) has been suggested to

originate from windblown soil and dust (Schroeder et al. 1987). Generally, aerosols from sea spray, dust, and volcanic mineral emissions tend to be larger than particles formed by condensation of gases in the troposphere (Buseck and Pósfai 1999). Skeaff et al. (2011) collected and analyzed particulates from the interior walls of primary stacks, enabling the quantitative chemical speciation of particulate releases from three copper smelters. Emissions from smelter stacks included copper species such as copper sulfate, copper arsenate as $(Cu_{0.94}Zn_{0.06})_2(AsO_4)(OH)$, $(Cu_{0.98}Zn_{0.02})_3(AsO_4)_2 \cdot 2H_2O$, or $(Cu_{0.84}Zn_{0.16})(AsO_3OH)$, and cuprite (Skeaff et al. 2011).

In a study of particulate matter emitted by fireworks, Hickey et al. (2020) sampled 10 types of fireworks and found that 4 of the 12 samples contained copper at concentrations of 12,000–53,000 ppm in the PM_{10} size range. Using an emission factor of 3,000 ppm developed by the European Copper Institute, Lifset et al. (2012) estimated that releases from fireworks in the United States increased from 40 metric tons in 1975 to 220 metric tons in 2000.

5.3.2 Water

Estimated releases of 173,311 pounds (~79 metric tons) of copper to surface water from 2,345 domestic manufacturing and processing facilities in 2022, accounted for about 0.72% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to waste water treatment and POTWs (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 333,462 pounds (~151 metric tons) of copper compounds to surface water from 1,561 domestic manufacturing and processing facilities in 2022, accounted for about 0.26% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to waste water treatment and POTWs (TRI22 2024). These releases are summarized in Table 5-5.

Sources of copper releases to water include algaecides, marine paints, corrosion of metallic copper, architectural uses, CCA wood management, industrial effluent, and copper mining leachate (Lifset et al. 2012).

Copper is a natural constituent of soil and will be transported into streams and waterways in runoff either due to natural weathering or anthropogenic soil disturbances (Rader et al. 2018). Sixty-eight percent of

releases of copper to water is estimated to derive from soil runoff and weathering, while copper sulfate use represents 13% of releases to water and urban runoff contributes 2% (EPA 1980b). In the absence of specific industrial sources, runoff is the major factor contributing to elevated copper levels in river water (Nölte 1988). In the previous EPA National Urban Runoff Program, 86 samples of runoff from 19 cities throughout the United States were analyzed, and copper was found in 96% of samples, at concentrations of 1–100 µg/L (equivalent to ppb) with a geometric mean of 18.7 µg/L (Cole et al. 1984).

Giusti 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 14–45x10^6 kg/year for copper in a dissolved form (e.g., rainwater) and 2–7x10^6 kg/year for copper in a particulate form (e.g., aerosols). Riverine input is estimated to be 10x10^6 kg/year as dissolved copper and 1,500x10^6 kg/year as copper bound to particulates.

Domestic wastewater is the major anthropogenic source of copper in waterways (Isaac et al. 1997; Nriagu and Pacyna 1988). Studies in Cincinnati, Ohio and St. Louis, Missouri showed discharges of copper into sewer systems from residential areas to be significant, with an average loading of 42 mg/person/day (EPA 1980b). 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/person/day. Concentrations of copper in influents to 239 wastewater treatment plants (12,351 observations) were 0.0001–36.5 ppm and the median value was ~0.4 ppm (EPA 1981a). Copper is not entirely removed in POTWs, and releases from these facilities contribute ~8% of all copper released to water (EPA 1980b). 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 the effluent of sewage treatment plants that discharged into the Providence River.

While some copper is removed from the waste stream by sewage treatment facilities, considerable copper remains in the effluent and is released into receiving waters (EPA 1980b, 1981b). Because removal efficiencies for copper from waste streams tend to remain constant rather than proportional to influent copper concentrations, increases in copper concentrations in POTW influent streams will also result in increased copper concentrations in the effluent streams (Isaac et al. 1997). The copper in domestic wastewater has been found to make up a substantial fraction of the copper found in POTW influent in the wastewater systems of four Massachusetts municipalities. The range of removal efficiencies reported for

pilot and full-scale plants suggests that removal depends strongly on plant operation or influent characteristics.

A source of copper released into waterways is from urban stormwater runoff. Copper in stormwater 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 µg/L of copper in stormwater runoff have been measured (Georgopoulos et al. 2001). Stormwater 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 released from disturbed soils contributes 68% of the copper released to waterways (Georgopoulos et al. 2001).

Experimental wastewater treatment technologies have been investigated with the goal to minimize copper contamination in finished water (Biswas and Mishra 2016; Shahin et al. 2019). Effluent guidelines set forth by the EPA are national wastewater discharge standards that are developed by EPA on an industry-by-industry basis. Copper limitations for 16 point-source categories are listed in the Effluent Limitations Guidelines and Standards Database. Values for copper limitations are 0.02–5 mg/L for daily maximums, 0.014–1.45 mg/L for the maximum range for monthly averages, and 0.15–2.07 mg/L for the monthly average range (EPA 2022c).

Overflow outfalls within combined sewer systems (e.g., combination of domestic and industrial wastewater plus stormwater) are the primary sources of 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 in the Newark Bay estuary. The mass loadings of copper into the estuary as a function of source are (in kg/day): discharges from the Passaic Valley Commission and Middlesex County Sewerage Authority, 126.5; municipal treatment systems, 103.4; stormwater runoff, 62.2; combined sewer overflows, 48.0; tributary flow, 39.1; and industry direct discharge, 8.82.

Wastewater generated from copper mining operations comes from seepage, runoff from tailing piles, or utility water used for mine operation. The amounts of wastewater generated were 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 1980a). Copper concentrations in wastewater from a selected open pit and underground copper mine were 1.05 and 0.87 ppm, respectively. Data regarding copper concentrations in wastewater associated with selected concentrating, smelting, and refining operations can be found in EPA (1980a).

Drainage from mining operations and abandoned mines has been shown to influence copper content in local surface waters with concentrations as high as 69,000 ppb being measured (Rösner 1998). An assessment of the life cycle of global sulfidic copper mine waste indicted that copper tailings, from large- and medium-sized copper deposits contribute to >75% of the global ecotoxicity impacts of copper tailings via leaching and infiltration. Analysis of data from 431 global active copper mine sites revealed concentrations of $Cu(OH)_2$ (mole/Kg) ranging from ~0.001%wt to ~0.09%wt in tailings from porphyry deposits, volcanic massive sulfide deposits, skarn deposits, sediment hosted deposits, magmatic sulfide deposits, iron oxide deposits, intrusion related deposits, and epithermal deposits (Adrianto et al. 2022).

Studies from the 1980s reported that effluents from power plants that use copper alloys in the heat exchangers of their cooling systems discharge copper into receiving waters (U.S. NRC 1984). The largest discharges occur after startup and decrease rapidly thereafter. At the Diablo Canyon Nuclear Power Station, a very high startup discharge containing 7,700 ppb of copper fell to 67 ppb after 24 hours (U.S. NRC 1980). During normal operation at two nuclear power stations $6.5x10^6$ m^3 (1,700 million gallons) of seawater per day is used as cooling water for these facilities and discharged into the ocean, with copper levels in the effluent of 0.6–3.3 ppb (U.S. NRC 1980). This amounts to a total output of copper in the discharged seawater of 3.9–42 kg/day or 1,400–15,000 kg/year from these two power plants. Except for after start-up of the cooling system, most of the soluble copper (that which passes through a 0.45-µm filter) discharged was in bound forms (U.S. NRC 1980). During normal operation, <20% of the copper released was in the <1,000 molecular weight fraction, which contains the more available copper species. More recent data on these releases were not located.

Copper sulfate is added directly 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; EPA 1980b). The reduction in dissolved copper during this period was accompanied by an increase in particulate copper (e.g., sorption to algae or other organic matter, which settles into the sediments of these bodies of water). The copper in the settled particulates is in equilibrium with the water column, which greatly favors copper in a bound state.

A potential source of copper release into waterways is leachate from municipal landfills. Copper concentrations in leachate obtained from 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; EPA 1980b; 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 should be made relative to the contribution of copper from surrounding soils, as determined from appropriately selected control samples.

Copper can enter surface waters because of agricultural runoff. For example, estimated loading rates of copper into surface water from irrigation water runoff near the Stillwater National Wildlife Refuge were 0.307–8.34 mg/hour, depending on what period of the irrigation season samples were taken (Kilbride et al. 1998). The highest loading rates were obtained during the middle period (August through mid-September) of the irrigation season. The copper in the runoff water was found to be predominantly bound to drift material in the water (e.g., algae, vascular plants, invertebrates, vertebrates, and detrital material).

5.3.3 Soil

Estimated releases of 9,866,050 pounds (~4,475 metric tons) of copper to soil from 2,345 domestic manufacturing and processing facilities in 2022, accounted for about 41.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 276,994 pounds (~126 metric tons), constituting about 1.15% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-4.

Estimated releases of 124,694,079 pounds (~56,560 metric tons) of copper compounds to soil from 1,561 domestic manufacturing and processing facilities in 2022, accounted for about 97.87% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 211,044 pounds (~96 metric tons), constituting about 0.17% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-5.

TRI data show that the largest release of copper compounds come from Utah and Arizona (TRI22 2024). Both states have active mining operations and the majority of the reported releases result from on-site disposal of tailings that are typically placed in secure holding areas. Facilities such as Kenncott Utah Copper Mine and Copper Smelter Refinery in Utah and Freeport-Mcmoran Copper & Gold and Pinto Valley Mine in Arizona account for the largest sources of copper released, both reporting release to onsite facilities (TRI22 2024).

An estimated 97% of copper released from all sources into the environment is primarily released to land (EPA 1980b). These include primarily tailings and overburdens from copper mines and tailings from mills. The copper in 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 (EPA 1980b). These wastes accumulate in mining states. Other releases to land include sludge from POTWs, municipal refuse, waste from electroplating, iron, and steel producers, discarded copper products (e.g., plumbing, wiring) that are not recycled, fungicides, animal feed, fertilizers, brake pads, vehicle leaks, and tire wear, and CCA-treated wood (EPA 1980b; Lifset et al. 2012; Tang et al. 2023). The copper content of municipal solid waste is ~0.16%. Much of this waste is landfilled directly or is in the form of residues following incineration. Emission factors in milligrams of copper released per gram of solid waste have been estimated for various industries. These factors would enable estimation of an industry's copper releases in terms of total 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 (EPA 1980b).

Some animal feeds contain trace metals including copper; excess copper from animal diets ultimately ends up in manure (Chesapeake Bay Foundation 2004). The land application of biosolids such as manure may result in a buildup of heavy metals such as copper in soils (Mahdy et al. 2007; Raven and Loeppert 1997). In Arkansas, daily production of poultry manure has been reported to contain 540 pounds (0.24 tonnes) of copper (United Poultry Concerns 2022). In accordance with 40 CFR Part 503, concentrations and loading rates of copper in sewage sludge are regulated as follows: ceiling concentration, 4,300 mg/kg; cumulative pollutant loading rate, 1,500 kg/hectare; monthly average concentration, 1,500 mg/kg; and annual pollutant loading rate, 75 kg/hectare per 365-day period (EPA 2018a).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

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), in-cloud scavenging (attachment of particles to rain droplets within clouds), and washout (collision and capture of particles by falling raindrops below clouds)

(Schroeder et al. 1987). The removal rate and distance traveled from the source depend on several factors, including source characteristics, particle size, turbulence, and wind velocity.

Gravitational settling governs the removal of large particles with mass median aerodynamic diameters >5 µm, 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 [µg/m^3]) for large particles displays a seasonal dependence that reflects more effective scavenging by snow than by rain (Chan et al. 1986). Copper from combustion sources is often adsorbed to sub-micron particulate matter. Thermal process may also release copper oxide or elemental copper as a vapor or copper adsorbed to larger particulates (EPA 1980b). Copper adsorbed to sub-micron particles remains in the troposphere for an estimated 7–30 days. In that time, some copper may be carried far from its source (EPA 1980b).

Rates of metal deposition (e.g., depositional fluxes) vary between dry and wet depositional processes and show spatial variability. Dry depositional fluxes of copper tend to be higher in highly urbanized areas and lower in less urbanized areas or areas with minimal anthropogenic activity. For example, average depositional rates were 0.06 mg/m^2/day in Chicago, Illinois, 0.007 mg/m^2/day in South Haven, Michigan, and 0.01 mg/m^2/day 6–10 km offshore of Lake Michigan (Paode et al. 1998). Estimated copper deposition rates in urban areas were 0.119 and 0.164 kg per hectare per year (kg/ha/year) or 0.0326 and 0.0449 mg/m^2/day for dry and wet deposition, respectively (Schroeder et al. 1987). Bulk deposition was 0.002–3.01 kg/ha/year or 0.0005–0.825 mg/m^2/day (Golomb et al. 1997; Landing et al. 1995; Schroeder et al. 1987). For rural areas, the range of bulk deposition was 0.018–0.5 kg/ha/year or 0.0049–0.1 mg/m^2/day and wet deposition was 0.033 kg/ha/year or 0.0090 mg/m^2/day. The washout ratio was 140–751 (Schroeder et al. 1987).

Levels of airborne copper measured at a rural site in Bondville, Illinois were comparable to regional background levels in other urban study sites with variations, such as episodic increases, depending on wind speed, direction, and location relative to local point sources, observed. Sources of copper in urban areas include coal combustion, soil, tire wear, and automobile emissions (Kim and Fergusson 1994). In one urban study at a site in East St. Louis, smelters were the primary source of copper. From this site, it was observed that copper depositional fluxes followed an exponential decay as one transitioned from the urban site to more rural settings (Sweet et al. 1993). In contrast, it has been observed that at more remote sites, atmospheric copper is derived from source points in nearby cities and depositional fluxes of airborne, windblown dust and soil containing this trace metal (Fergusson and Stewart 1992).

Furthermore, high copper concentrations in snow and aerosols from polar snowfields and remote locations have been attributed to airborne pollution and long-range transport (Annibaldi et al. 2007; Dinu et al. 2020).

Long-range transported emissions from combustion processes are typically associated with fine particles; however, there can be instances where the highest concentrations of copper are measured in coarse particles near point sources (Paode et al. 1998). Estimates of depositional velocities for fine particles (<2.5 µm) and coarse particles (2.5–10 µm) in urban (Chicago) and rural (Kankalee, Illinois) areas have been made (Pirrone and Keeler 1993). The estimated depositional velocities are urban, 0.25–0.46 rcm/second and rural, 0.18–0.25 cm/second for fine particles; and urban, 1.47–2.93 cm/second and rural, 0.87–1.71 cm/second for coarse particles. The differences in depositional velocities are thought to be due to higher surface roughness and wind velocities in Chicago.

Copper concentrations in particulates formed in a controlled study of waste oil combustion were: 687±11 µg/g (10-µm diameter), 575±8 µg/g (50-µm diameter), 552±12 µg/g (100-µm diameter), 568±9 µg/g (300-µm diameter), and 489±8 (500-µm diameter). Approximately 25% of copper was in the 10-µm fraction and ~18% was in each of the larger fractions (e.g., 50-, 100-, 300-, and 500-µm diameter) (Nerín et al. 1999).

Water. Copper in aqueous environments exists primarily in ionic form as Cu(II) and is weakly associated with water molecules. Copper may also be adsorbed or associated with suspended particles or various organic and inorganic chemicals in aqueous systems (EPA 2007). Free copper ions have the greatest bioavailability in water (Wapnir 1998). The mobility and bioavailability of copper in water and sediments depend on the physical and chemical form, which is a function of environmental conditions such as temperature, pH, and redox conditions; copper speciation and solubility of the copper form; and types of complexes that may be formed with other chemicals present (both organic and inorganic) (Adams et al. 2020; Ankley et al. 1996; Harmesa et al. 2023).

The average concentrations of copper in Lakes Superior, Erie, and Ontario were 760, 870, and 830 ng/L, respectively, in studies from the late 1990s and early 2000s (Georgopoulos et al. 2001; Nriagu et al. 1996). These values were derived from measurements taken from 11, 11, and 9 nearshore and offshore sampling sites at different points in the water column up to depths of 251, 55, and 145 m for Lakes Superior, Erie, and Ontario, respectively (Nriagu et al. 1996). In Lake Ontario, the highest copper concentrations were found at nearshore sampling sites neighboring Buffalo, New York (887–1,051 ng/L),

Rochester, New York (1,041–1,098 ng/L), and Kingston, Ontario (921–1,026 ng/L). The lowest concentrations of copper in Lake Ontario were measured in an offshore sampling site (540–710 ng/L) that was approximately 40 km from the Buffalo sampling site.

The atmospheric input of copper into the Great Lakes is 330–1,470 ng/m^2/year, which amounts to a total deposition of 8.00–35.6x10^{13} ng/year (80.0–356 kg/year). This input of copper accounts for 60–80% of the anthropogenic input into Lake Superior and for 20–70% of the anthropogenic input into Lakes Erie and Ontario (Georgopoulos et al. 2001; Nriagu et al. 1996).

Much of the copper discharged into waterways is bound to particulate matter and settles out. In the water column and in sediments, copper adsorbs to organic matter, hydrous iron and manganese oxides, and clay. In the open water column, a significant fraction of the copper is adsorbed within the first hour of introduction, and in most cases, a steady state is obtained within 24 hours (U.S. NRC 1984). Most dissolved copper in POTW effluent and surface runoff is mostly already in complexed form (Sedlak et al. 1997). Copper in wastewater discharged into Back River leading into Chesapeake Bay, Maryland contained 53 ppb of copper, of which 36 ppb (based on weight) were in the form of settleable solids (Helz et al. 1975). The concentration of copper rapidly decreased downstream of the outfall so that 2–3 km from the outfall, the copper concentration had fallen to 7 ppb. The concentration of copper in sediment 2–3 km downstream from the outfall was about a factor of 10 higher than in uncontaminated areas (e.g., Rappahannock River). Based on their data and the results from other studies, Helz et al. (1975) estimated that approximately 200 metric tons of copper entered the Chesapeake Bay from the effluent discharged from waste treatment plants annually. Whitall et al. (2010) concluded that copper released from antifouling paint on boats was a likely source of copper measured in the Choptank River estuary, a tributary of the Chesapeake Bay.

Copper binds primarily to organic matter in aerobic estuarine sediment unless the sediment is low in organic matter content. Davies-Colley et al. (1984) determined copper's absorptivity to model phases in artificial seawater to estimate copper distributions between estuarine sedimentary phases and water. The model 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 binding 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 the salinity was reduced from 35 to 5%. Considering the

typical compositional characteristics of estuarine sediment in terms of binding capacity, the results indicate that copper binds predominantly to organic matter (humic material) and iron oxides. Manganese oxide contributes only 1% to the binding because of its generally low concentration in sediment; the other phases are usually unimportant. These findings concur with results of selective extraction experiments (Badri and Aston 1983) and studies of the association of copper with humic material (Raspor et al. 1984). Copper will bind with acid-volatile sulfide to form very insoluble sulfur precipitates in sulfidic anoxic sediments, which is an important environmental fate process in marine sediments that are often anaerobic (Ankley et al. 1996; Di Toro et al. 1996; Rader et al. 2019). Copper has been reported to have a higher affinity for sulfide than other trace metals such as nickel, cadmium, and zinc (Rader et al. 2019).

Sorption capacity of copper to aquatic microplastics was evaluated in a review using experimental data and artificial neural networks modeling (Guo and Wang 2021). The study authors found that sorption capacity was influenced by the concentration of metal ions in the surrounding waters and increased as levels of the ion increased; predicted sorption capacities for copper based on concentrations in South Asia, South Africa, and China were 270–280 μg/g. Furthermore, sorption capacity is related to salinity and pH, where increased salinity decreases the sorption capacity, and values of <0.3 μg/g are predicted for the Pacific Ocean, Arctic Ocean, and Southern Ocean; along the China coastline, sorption of copper onto polypropylene microplastics was ~0.117–0.174 μg/g. Findings also indicated that aged microplastics demonstrate a sorption capacity for metal ions 1–5 times higher than virgin microplastics.

Soil. Most copper deposited on soil from the atmosphere, agricultural use, and solid waste and sludge disposal is retained in the upper 5–10 cm of soil in comparison to lower soil depths, except in sandy soils where the lability of bound copper is greater (Breslin 1999; EPA 1980b; Giusquiani et al. 1992; Hutchinson 1979; Luncan-Bouché et al. 1997; Levy et al. 1992). Copper was evaluated in soil samples at constructed wetlands on the Savannah River, South Carolina receiving storm runoff and industrial effluent generated from the Tritium Facility. Sediment core samples were collected twice a year from 2007 to 2013. Concentrations in surface sediments fluctuated over the study period and ultimately increased from 6.0±2.8 to 139.6±87.7 mg/kg dry weight. Concentrations of copper were lower in the middle and bottom layers of sediment at 5.2±5.8–19.7±43.0 and 4.4±1.4–7.4±7.5 mg/kg, respectively (Elhaj Baddar et al. 2021). 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 (DOI 1986; EPA 1979; Janssen et al. 1997; Petruzzelli 1997; Tyler and McBride 1982). Sandy soils with low pH have the greatest potential for leaching. In a laboratory study, Luncan-Bouché et al. (1997) demonstrated that 55–85% of

copper bound to sand (with no other soil components added) 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 (DOI 1986; Elliott et al. 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). Soil microorganisms also affect the absorption of copper in soils due to the uptake and assimilation of the metal by these microorganisms (Rieuwerts et al. 1998). Tang et al. (2023) demonstrated that in CCA-polluted soils, the levels of water extractable copper and bioavailable copper, free copper ion activity, and microbial inhibition decreased with increased cation exchange capacity, decreased the carbon to nitrogen ratio, and increased total nitrogen and total phosphorus in tested systems. However, it is not known how the rate of uptake and absorption capacity of the microorganisms for copper compares with the binding capacity and affinities of copper by organic matter in soils, such as humic and fulvic acids. When the amount of organic matter is low, the mineral content or iron, manganese, and aluminum oxides become important in determining the adsorption of copper. DOI (1986) reported that, in oxidized estuarine sediment, adsorption of copper is dominated both by amorphous iron oxide and humic material.

Copper binds strongly to soils with high organic content (14–34% organic matter, dry weight), and the distribution of copper in the soil solution is less affected by changes in pH (within the range of pH normally encountered in the environment) than other metals are (Gerritse and Van Driel 1984). In a laboratory study of competitive adsorption and leaching of metals in soil columns of widely different characteristics, copper eluted in a 0.01-M $CaCl_2$ leaching solution much more slowly and in much lower quantities than zinc, cadmium, and nickel from a low-pH and a high-pH mineral soils and not at all from peat soil, which contained the greatest amount of organic matter (Tyler and McBride 1982). Elliott et al. (1986) investigated pH-dependent adsorption of the divalent transition metal cations cadmium, copper, lead, and zinc in two mineral soils (silty clay loam, 0.5 g/kg organic dry weight, and sandy clay, 1.6 g/kg organic) and two soils containing considerable organic matter (loamy sand, 20.5 g/kg organic, and silt loam, 42.5 g/kg organic). Adsorption increased with pH, and copper and lead were much more strongly retained than cadmium and zinc. Reduction in absorptivity after removal of the organic matter demonstrated the importance of organic matter in binding copper. In a study of clay soils, Wu et al. (1999) observed preferential copper binding to organic matter but found higher binding affinities to fine (<0.2 μm) clay fractions once the organic matter had been removed.

To determine the factors affecting copper leachability 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 soil horizons, 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 leachability only in the oxidizing environment. In the reducing environment, the mobility was low, possibly due to the formation of sulfides.

The mobility of copper from soils was also found to increase following the introduction of 10–100 mM sodium chloride or calcium magnesium acetate deicing salts into soil (Amrhein et al. 1992). The concentration of sodium chloride or calcium magnesium acetate used in the study approximate those in runoff water produced from the melting of snow along salted roadways.

For concentrations up to 2 mg of copper per liter of water, 25–75% of copper entering POTWs is removed in sludge, much of which is disposed of by spreading on land. Thus, it is useful to ascertain whether copper in sludge is apt to leach into soil. This did not appear to be the case: leachate collected from sludge-amended soil contained <12 ppb of copper (EPA 1980b). Older studies found that small amounts of copper were found in leachate from soils treated with copper-containing sludge, and copper is typically confined to the upper 5–10 cm of soil (Breslin 1999; Davis et al. 1988; Giusquiani et al. 1992; Ritter and Eastburn 1978). In soils receiving long-term, heavy applications of sludge, high copper concentrations (471 mg/kg in comparison to 19.1 mg/kg in unamended control soils) were reported to depths of up to 25 cm (Richards et al. 1998). Brown et al. (1983) found that copper remained in the upper 12.7 cm of soil treated with sewage sludge for a year. 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 of copper due to the increased binding capacity provided by the “low metal” organics in the sludge (Petruzzelli et al. 1994). From the results of other work, the major portion of the copper (40–74%) is expected to be associated with the organic iron-manganese-oxide and carbonate fractions of most soils (Ma and Rao 1997).

Recent studies on the long-term effects of soil treated with organic amendments, such as sludge, manure, and compost, on copper availability have been published. Models to predict copper bioavailability in soils have been developed to characterize potential toxicity to ecological species under certain environmental conditions (Smolders et al. 2009). It has been observed that abiotic soil properties,

including the cation exchange capacity, pH, and composition, are significant factors in determining the available concentration of copper. The availability of copper species from freshly amended soils and aged field-contaminated, naturally leached soils is dependent on ionic strength and pH. Toxicity to ecological species was observed to be lower in experimentally aged or field-contaminated soils. Higher ionic strength and lower pH of freshly amended soils may create a more favorable environment both abiotically and biotically and increase metal bioavailability (Smolders et al. 2012). Smolders et al. (2012) found that copper availability in soil treated long-term with organic amendments was lower than that in soil that had been freshly spiked with Cu^{2+} salts due to its lower availability in the original matrix and to aging reactions. Cagnarini et al. (2021) simulated long-term metal concentrations in soil treated with organic amendments in Switzerland. Copper concentrations have decreased over time and are projected to remain nearly constant or in decline through 2100 (Cagnarini et al. 2021). The model suggests that although concentrations of copper in soil treated with sewage sludge are expected to decrease, historic inputs of sewage sludge would result in exceedances of the threshold concentration that would persist through 2100. Copper availability in soil to which stabilized sewage sludge or biosolids were applied has also been studied; concentrations of copper in biosolid treated clay, calcareous, and sandy soil were significantly higher than in control samples (Mahdy et al. 2007).

Other Media. Accumulation of copper in biota is inversely related to exposure concentrations (McGeer et al. 2003). Low potential for bioaccumulation is likely the result of natural homeostatic controls in organisms. Homeostatic regulation in a marine thornfish, *Terapon jarbua*, exposed to waterborne (10.6±1.2 µg/L copper) and dietary copper (162±10.4 µg/g dry weight) was investigated using a PBPK model (Wang and Wang 2016). Results from the study found that concentrations in the blood were lowest and increased minimally during exposure, while concentrations in the liver were highest and increased to levels as high as 10.1 and 8.4 µg/g fresh weight for dietary and waterborne exposures, respectively.

In multiple studies conducted prior to 1980, bioconcentration factors (BCFs) of copper in fish obtained in field studies were 667 in marine fish and 50–200 in freshwater fish, suggesting a low potential for bioconcentration (EPA 1980b). The BCF is higher for mollusks such as hard-shell clams and squid, with BCFs of 30,000 and 2.1×10^7, respectively; it was noted that the high levels found in squid may be a result of copper requirements for metabolic processes (EPA 1980b). This may present a major dietary source of copper that could be of concern for those individuals who regularly consume oysters, clams, or squid. Since mollusks are filter feeders and copper concentrations are higher in particulates than in water, this is to be expected (EPA 1980b). For example, 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), respectively, in their muscle tissue. The biomagnification ratio (the concentration of copper in fish compared to that in their potential food sources on a wet weight/wet weight basis) was <l, indicating no biomagnification in the food chain. The copper content of muscle tissue of fish from copper contaminated lakes near Sudbury, Ontario, did not differ significantly from that of the same fish species in lakes far from this source (Bradley and Morris 1986). In a commercial catfish pond where copper was applied as an algaecide, only 0.01% of the copper applied was taken up by the fish (Liu et al. 2006). Similarly, the copper concentration in shrimp in a shrimp farm with high copper bioavailability did not differ from other shrimp populations (Lacerda et al. 2009).

Copper ions have the greatest bioavailability in water; however, chemical speciation of copper is contingent on aqueous conditions, which may lead to differences in bioavailability (Erickson et al. 1996; Wapnir 1998). The bioavailability and uptake of copper in aquatic species vary with the physiochemical conditions present in the aquatic environment as well as the copper species present. For example, copper and copper monohydroxide binding capacity with dissolved organic matter in aqueous systems varies with the composition of the dissolved organic matter, which affects the bioavailable concentrations present (Davies-Colley et al. 1984; EPA 2007; Hollis et al. 1997). Models such as the Biotic Ligand Model and others have been developed to predict the uptake and aquatic toxicity of copper by considering parameters that affect the bioavailability of copper (e.g., dissolved organic carbon, hardness, and pH) (Adams et al. 2020; Brix et al. 2017; Di Toro et al. 2001; EPA 2007). De Schamphelaere et al. (2009) evaluated the composition of dissolved organic matter and corresponding aquatic toxicity (48-hour EC_{50}) values of copper for the aquatic invertebrate, *Daphnia magna*. Dissolved organic carbon concentrations varied between 2 and 18 mg/L, with corresponding EC_{50} values of between 51 and 638 µg Cu/L. These results suggested that lower dissolved organic carbon results in an increase in bioavailable copper (De Schamphelaere et al. 2009).

As with water, the bioavailability of copper in food sources and other environmental media is a function of the conditions, solubility, copper speciation, and types of complexes that may result. Possible ligands in foods may include amino acids and other organic acids that can act as strong or weak complexing ligands affecting the bioavailability of copper in the complex formed. Soil and sediment composition and characteristics are also factors in determining the copper complexes that may be formed; for example, humic and fulvic acids are potential ligands (Adams et al. 2020; NRC 2000; Tipping 1994; Wapnir 1998).

The bioavailability of copper from different compounds has been studied in chickens. Baker et al. (1991) compared copper bioavailability from copper oxide, cuprite, and copper-lysine complex to that of $CuSO_4 \cdot H_2O$ and found that accumulation of copper in the liver from cuprite and copper-lysine complex is comparable to $CuSO_4 \cdot H_2O$, while copper in copper oxide was not readily bioavailable (Baker et al. 1991).

No evidence of bioaccumulation was obtained from a study of various pollutants in the muscle and livers of 10 mammal species in Donana National Park in Spain (Hernandez et al. 1985). The park is impacted by organochlorine compounds and heavy metals emitted from anthropogenic activities that surround the park. For example, the Guadalquivir River that flows through the park first flows through a major mining region in addition to a large urban area and industrial areas, potentially carrying with it contaminants acquired from these sites. The animal species in the study 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. Likewise, in a study of a food web in a beech tree forest in Northern Germany, there was no evidence of biomagnification in tertiary consumers (e.g., vole, shrew, and mouse) compared to secondary consumers (e.g., earthworm, snail, beetle, and isopod) (Scharenberg and Ebeling 1996). 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. Apparently, copper was not bioaccumulating in the food chain of the rabbit (Dressler et al. 1986).

Trophic transfer factors (TTFs), which are similar to biomagnification factors, were investigated for copper in freshwater and marine food chains (Cardwell et al. 2013). Copper TTFs in freshwater were 0.1 for cladocera, 1.0 for insects, 6 for gastropods, and 27 for bivalves. Copper TTFs in marine studies were 0.3 for amphipods, 1.4 for bivalves, and 0.1 for fish. TTFs for accumulator species in marine systems ranged from ~0.2 for *Perna viridis* to ~8.1 for *Saccostrea glomerata*. The relationship between the presence or absence of adverse effects, calculated TTFs, and dietary exposure concentration from laboratory studies for copper showed that only one of the nine data points associated with effects had a TTF >1.0, the value in which, if exceeded, suggests the potential for trophic transfer and biomagnification (Cardwell et al. 2013).

At the lowest levels of the food chain, there is little evidence of copper bioaccumulation. In a study of copper uptake in earthworms as a function of copper concentration (6–320 mg/kg dry weight) in sludge-

amended soils, a BCF of <1 (0.67) was obtained (Neuhauser et al. 1995). In another example, a study of earthworms and soil from 20 diverse sites in Maryland, Pennsylvania, and Virginia, copper concentrations in earthworms showed a poor correlation with that in soil (Beyer and Cromartie 1987). These results are consistent with the results of another study that also showed no clear correlation between copper concentrations in earthworm tissues and two soils that were heavily contaminated with heavy metals (copper concentrations of 242 and 815 mg/kg dry weight) (Marinussen et al. 1997).

However, there is some evidence in one study for bioconcentration of copper at low copper concentrations in soil. Even though Scharenberg and Ebeling (1996) showed that there was no evidence for biomagnification of copper in a forest food web, their results did show that the total concentrations of copper in the secondary (18.3–192.0 mg/kg dry weight) and tertiary consumers (9.9–17.4 mg/kg dry weight) were higher than the concentrations of the metal in the dominant vegetation (5.3–10.9 mg/kg dry weight) and soil (1.8–5.8 mg/kg dry weight) in the ecosystem.

Diks and Allen (1983) added copper to four sediment/water systems and studied the distribution of copper among five geochemical phases, namely, absorbed/exchangeable, carbonate, easily reducible (manganese oxides and amorphous iron oxides), organic, and moderately reducible (hydrous iron oxides). 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. This result suggests that the redox potential and pH in the gut of the worm is such that manganese oxide coatings are dissolved. The copper derived from the dissolved manganese oxide phase in the gut of the tubificid worms appeared to be soluble and available for uptake.

5.4.2 Transformation and Degradation

Air. Data are available on the speciation of copper in airborne particulates. It is generally assumed that metals of anthropogenic origin, especially those from combustion sources, exist in the atmosphere as oxides because metallic species are readily attacked by atmospheric oxidants. As these oxides age, sulfurization may occur, but only when SO_X gases are present in the atmosphere in sufficient amount. For example, in Arizona, atmospheric copper oxide levels near copper smelters were strongly correlated with co-emitted sulfur (Schroeder et al. 1987). Copper was primarily bound to organics and sulfides in dry deposition near a smelter in China, and dust from the smelter and in deposition samples showed sulfides and oxides (Liu et al. 2021c). Copper has been observed bound to fine aerosol particles as the sulfate and

nitrate (Osán et al. 2010). The form of copper in the coarse fraction could be used to trace its source to soil resuspension or brake pad wear erosion (Osán et al. 2010).

In fog water, Cu(II) is reduced to Cu(I) by sulfite, which becomes enhanced by the fact that sulfite is also a ligand of and binds to Cu(I) (Xue et al. 1991). Concentrations of Cu(I) in fog water were 0.1–1 μM, or 4–>90%, respectively, of copper in the Cu(I) state. The reduction of Cu(II) to Cu(I) is pH-dependent and occurs rapidly at pH >6 (Xue et al. 1991).

Water. Free Cu(I) (Cu^{+}) ion is unstable in aqueous solution, tending to disproportionate to Cu(II) (Cu^{2+}) and copper metal unless a stabilizing ligand is present (EPA 1979; Kust 1978; Tipping 1994). The only cuprous compounds stable in water are insoluble ones such as copper (I) sulfide, copper (I) cyanide, and copper (II) fluoride. Therefore, human exposures to copper will predominately be in the form of Cu(II). Copper in its Cu(II) state forms coordination compounds or complexes with both inorganic and organic ligands. Ammonium and chloride ions can form stable ligands with copper. Copper also forms stable complexes with organic ligands such as humic acids, binding to -NH_2 and -SH functional groups and, to a lesser extent, with -OH functional groups. Copper binding to humic and fulvic substances appears as both ionic binding and chelation. 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). In water, the presence of ligands may affect other physicochemical processes such as adsorption, precipitation, and oxidation-reduction (EPA 1979). More specific information on the transformation and degradation of copper in its cupric [Cu(II)] and cuprous [Cu(I)] states is given below.

At the pH values and carbonate concentrations characteristic of fresh surface waters, most dissolved Cu(II) exists as carbonate complexes rather than as free (hydrated) cupric ions (Stiff 1971).

Based on the results of a theoretical model, the major species of soluble copper found in freshwater, seawater, and a 50:50 combination of the freshwater and seawater over a pH range of 6.5–7.5 is Cu^{2+}, $Cu(HCO_3)^{+}$, and $Cu(OH)_2$ (Long and Angino 1977).

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^{2+}, Fe^{2+}, Mg^{2+}, etc.), anions (OH^{-}, S^{2-}, PO_4^{3-}, CO_3^{2-}), and soluble cupric-organic and -inorganic complexing agents. If the combination of a particular anion with copper forms an insoluble salt, precipitation of that salt will occur. The most significant precipitate

formed in fresh surface waters is malachite ($Cu_2[OH]_2CO_3$) (Sylva 1976). Other important precipitates are $Cu(OH)_2$ (and ultimately CuO) and azurite ($Cu_3[OH]_2[CO_3]_2$). In anaerobic waters, Cu_2S, cuprite, and metallic copper forms and settles out (EPA 1979). The combined processes of complexation, adsorption, and precipitation control the level of free Cu(II) in water. The chemical conditions in most natural water are such that, even at relatively high copper concentrations, these processes will reduce the free Cu(II) ion concentration to extremely low values.

As a result of the previously described 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 soluble fraction of copper in water is usually defined as that which will pass through a 0.45-µm 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 (e.g., the relative ability of the copper to dissociate from the bound form to the free ion) of the copper forms in the water. Categories range from the very labile metal (e.g., free metal ion, ion pairs, inorganic or organic complexes) to slowly or nonlabile metal (e.g., colloidally bound to inorganic colloidal phases of other metals such as $Fe(OH)_3$ or FeOOH, or bound to high molecular weight organic material) (Tan et al. 1988). For example, in a typical study, 18–70% of dissolved copper in river water was labile and 13–30% was slowly labile (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 (U.S. NRC 1984). Newer technologies include hyphenated inductively coupled plasma-mass spectrometry (ICP-MS) (Agilent Technologies 2012). The resulting classification depends on the specific procedure employed. Therefore, a comparison of the results of different researchers should be done in general terms.

The nature of copper's association with inorganic and organic ligands will vary depending on the pH, copper concentration, concentration of competing ligands, binding capacity of the ligands, and hardness or salinity of the water (Adams et al. 2020; Breault et al. 1996; Cao et al. 1995; Gardner and Ravenscroft 1991; Giusti et al. 1993; Lores and Pennock 1998; Tipping 1994; 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

$CaCO_3$), inorganic species like CO_3^{2-} and OH^- were the most important ligands at high copper concentrations (McCrady and Chapman 1979). However, other species such as organic compounds were important at low copper concentrations. On the other hand, copper in samples from surface water of lakes and rivers in southern Maine with a relatively low pH (4.6–6.3) and alkalinity (1–30 ppm as $CaCO_3$) was largely associated with organic matter (Giesy et al. 1978). The binding of copper to dissolved organics was found to be dependent on the specific organic chemical species (e.g., fulvic acid) and their concentrations in the surface water, the number of available 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 depression of the solubility of high molecular weight fulvic acid in the presence of calcium and magnesium ions than to competition of these ions with copper for fulvic acid binding sites. Changing pH from 8 to 6 resulted in a 7-fold increase in the 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 copper binding in lakes and rivers than did dissolved organic matter (Truitt and Weber 1981). A green precipitate, confirmed to be malachite ($Cu_2[OH]_2CO_3$), was formed in river water in Exeter, New Hampshire. The water had a high alkaline pH (7.4) with 43.5 mg/L $CaCO_3$ as a buffering agent that was higher than six other surface waters (e.g., three rivers, two reservoirs, a pond, and a swamp) with pH values of 5.7– 7.4 and 1.7–41 mg/L, respectively. A computer simulation of the copper species in water of a pond and water obtained from an artesian well that fed the pond predicted that 98% of the copper in the artesian well water would exist as the free copper ion (Cu^{+2}), 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). These estimates were based on experimentally determined binding capacities of the organic matter in the two water sources and stability constants for the copper-organic matter complexes.

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. The Fields Point waste treatment facility accounts for 90% of the copper input into the bay through the Providence River, with dissolved copper representing 60% of the total copper input. The concentrations of dissolved and organic copper were 16.4 and 2.3 µg/kg, respectively, in the Providence River and 0.23 and 0.12 µg/kg, respectively, in Rhode Island Sound. Particulate copper

concentrations in Narragansett Bay were 0.06–2.42 µg/kg and generally comprised 40% of the total copper in the bay. Analysis of the data indicated that ~75% of the dissolved copper that enters the bay from the Providence River is removed within the bay.

Organic ligands can 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 ocean surface 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 biological origin. A second, weaker class of organic ligand was of geologic origin. An independent study showed that copper binds to humic material at several sites. The binding strength of the sites varied by 2 orders of magnitude (Giesy et al. 1986). The humic material in this 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 (U.S. NRC 1980). Ten to 75% of the discharged copper was in particulate form. Chemical speciation in environmental media where the binding of copper to organic ligands depends on organic matter in the system may be estimated using models such as WHAM (Windermere Humic Aqueous Model) (Tipping 1994).

The bioavailability of Cu(I) is difficult to access due to its thermodynamic instability in the environment (Xue et al. 1991). Cu(I) is a reactive reducing agent, and its concentrations in the environment is typically determined both by its reaction with oxygen and other oxidants in the aqueous environment to form Cu(II) and its rate of production through the reaction of Cu(II) with reducing agents (Sharma and Millero 1988). Investigators have shown the presence of Cu(I) in seawater, which is thought to occur through the reduction of Cu(II) to Cu(I) by photochemical processes (Moffett and Zika 1987; Xue et al. 1991). The detection of Cu(I) in seawater is likely the result of the stabilization of Cu(I) through complex formation with chloride ions. Cu(II)-organic complexes absorb radiation at wavelengths >290 nm and can undergo charge transfer reactions where the Cu(II) is reduced and a ligand is oxidized. Photochemically-generated reducing agents such as O^{2-} and H_2O_2 in the surface water of oceans and possibly other natural waters (e.g., lakes) may contribute to the reduction of Cu(II) to Cu(I) in these waters (Moffett and Zika 1987; Sharma and Millero 1988).

Melake et al. (2023) measured the average concentration of copper in water (176.43 µg/L) and fish tissues (*Oreochromis niloticus*, *Clarias gariepinus*, and *Bacteroides intermedius*) and calculated bioaccumulation factor (BAF) values of 0.0002–0.004.

Cu(I) was measured in sunny waters off the Florida coast at depths up to 90 m. Cu(I) concentration was highest in the surface layer of seawater, accounting for ~15% of the total copper (~$4x10^{10}$ mol/L), and the hydrogen peroxide concentration increased in parallel to that of Cu(I) (Moffett and Zika 1987). Concentrations of Cu(I) were ~1.2 $x10^{10}$ mol/L at 25 m and decreased to below the detection limit at 90 m (<$0.1x10^{10}$ mol/L). In addition, the percentage of free Cu(I) is highest on the surface. 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 higher salinity) (Sharma and Millero 1988). 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 (Sharma and Millero 1988).

Sediment and Soil. The adsorption of copper to soil and sediment was discussed in Section 5.4.1 under transport and partitioning. It is important to understand the transport and fate of copper and its compounds in soils and sediments because these compartments tend to be large reservoirs of copper and could have an impact on human exposures. Copper concentrations in drinking water obtained from groundwater can be affected by the leaching of copper from soil. Reservoir sediments have been shown to be sources of copper in drinking water (Georgopoulos et al. 2001). Although much of the copper is bound to inorganic or organic matrices in soils and sediments, there is the potential for release of copper into pore water within soils and sediments depending on soil conditions and the forms of the copper present. There is evidence to suggest that copper binding in soil is correlated with pH, cation exchange capacity, organic content of the soil, presence of manganese and iron oxides, and even presence of inorganic carbon such as carbonates (Petruzzelli 1997; Rieuwerts et al. 1998). At pH levels >5, absorption of copper from pore water onto soil components becomes a significant process, whereas at pH levels <5, copper largely remains in pore water and is, therefore, mobile in soil (EPA 1980b). However, broad generalizations about the mobility of copper in soils are not possible since the situation will differ among different soil types and environmental conditions. More specific information on the lability (e.g., extractability) of copper from differing soils and conditions follows.

There are several ways for determining the forms of copper in soil, the most common method being measuring of the extractability of the copper with different solvents. Extractability is a function of 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 can occur, as well as other transformations. 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 potassium chloride. 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 of the 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 coefficients for copper were >64 for mineral soils and >273 for organic soils. Of the eight heavy metals in the study, only lead and antimony had higher partition coefficients than copper. Most of the copper in Columbia River estuary sediment and soil was associated with inorganic carbon (e.g., carbonate), but not with the amount of extractable iron or the organic carbon content of the sediment (DOI 1986).

The amount of ammonium acetate- and diethylenetriaminepentaacetic acid (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 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 of copper partitioning 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 the 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, 69–74.4% 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), 97.6–99.6% of the copper was found to be associated with the residual fraction.

In estuarine environments, anaerobic sediments are known to be the main reservoir of trace metals. Under anaerobic conditions, Cu(II) salts will reduce to Cu(I) salts. The precipitation of cupric 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 (i.e., the copper is removed from water and held in the sediment as an insoluble cuprous sulfide). 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 generally is associated with fine sediment, as opposed to coarse sediment. Badri and Aston (1983) 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 (manganese and iron oxides and possibly carbonates); and resistant (lithogenic). In the three sediments, the non-lithogenic fraction accounted for ~14–18% of the total copper and the easily exchangeable component was 5% of the total copper. In addition, the compositional associations of copper in sediment samples taken from western Lake Ontario were analyzed employing a series of sequential extractions (Poulton et al. 1988). The mean (±standard deviation) percentages of copper in the various fractions were exchangeable, 0±0; carbonate salt, 0.1±0.3; iron or manganese oxide-bound, 0.2±0.3; organic-bound, 40±11; and residual, 60±8. Another study found that 10–20% of the copper in Lake Ontario sediment samples was bound to humic acids, with virtually all the copper 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.

Melake et al. (2023) measured the average concentration of copper in sediment (32.93 mg/kg dry weight) and in fish tissues (*O. niloticus*, *C. gariepinus*, and *B. intermedius*) and calculated biota-sediment accumulation factor (BSAF) values of 0.001–0.02.

Other Media. Copper is an essential nutrient for plant growth and metabolism. Therefore, uptake of copper from soil by plants through the roots is a natural and necessary process, actively regulated by the plant (Clemens 2001). However, loss of biodiversity has been reported in environments contaminated with copper. Naveed et al. (2014) found that increasing copper pollution resulting from a former wood preservation plant had a negative impact on plant growth and species. Earthworms, bacteria, nematodes, and fungi showed a similar response to increasing copper concentrations. Results of this study showed that there was a 10% loss in soil biodiversity within a copper concentration range of 110–800 mg/kg (Naveed et al. 2014). Cao et al. (2020) observed a reduction in soil enzyme activity and both microbial and fungal diversity in copper-amended soils (measured concentrations of 19.8, 173.7, and 468.9 mg/kg)

under flooded and non-flooded conditions over a 60-day period; high concentrations of copper showed significant decreases in the number and diversity of the communities. Furthermore, fungal communities were more sensitive than bacteria under flooding conditions (Cao et al. 2020).

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, this is determined by copper concentrations in soil, soil type, soil components, pH, oxidation-reduction potential of the soil, concentrations of other cations and anions in the soil, etc. (Rieuwerts et al. 1998). Other factors involved root surface area, plant genotype, stage of plant development, weather conditions, interaction with other nutrients in the soil, and the water table (Gupta 1979). Using lime (calcium carbonate) to adjust soil pH is another factor that affects copper uptake. For example, liming acidic soils can increase copper uptake in hay, but decrease copper uptake in wheat (Gupta 1979). However, the effect of liming on increasing soil pH does not appear to be the overriding factor behind the changes in copper uptake by plants, even though there is evidence that the addition of lime to soil to increase the pH to 7 or 8 reduces copper bioavailability to some plants (EPA 1980b). This is evidenced by the fact that changes in pH (5.4–8.0) have little effect on copper concentrations in plant tissues (Gupta 1979).

It appears that microorganisms can transform copper and affect the copper bioavailable for plant uptake (Mulder and van Veen 1968). Hydrogen sulfide (H_2S)-forming microorganisms may be involved in soil copper precipitation as nearly insoluble sulfide salts. Bacteria of the genera, *Thiobacillus* and *Ferrobacillus*, can oxidize CuS to copper sulfate. Johnson et al. (2017) carried out experiments to study the redox transformation of copper by acidophilic bacteria and found that oxidation and reduction of copper were mediated by acidophilic bacteria indirectly. Copper (I) accumulated in aerobic cultures of sulfur-grown *Acidithiobacillus* spp. More copper (I) was produced by *Acidithiobacillus caldus* than by the other species. Reduction of copper (II) by aerobic cultures of sulfur-grown *Acidithiobacillus* spp. was more pronounced as culture pH declined. *Acidithiobacillus* grown anaerobically on hydrogen and *Acidiphilium cryptum* grown micro-aerobically on glucose only reduced copper (II) when iron (III) was included. Copper (I) was only oxidized by growing cultures of *Acidithiobacillus* spp. when iron (II) was included.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-9 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-10.

Table 5-9. Lowest Limit of Detection for Copper Based on Standards[a]

Media	Detection limit	Reference
Metal and nonmetal dust on mixed cellulose ester membrane (MCE) filters in workplace	0.07 µg/sample[b]	NIOSH 2014a; Method 7302, Issue 1
Metal and nonmetal dust on polyvinyl chloride (PVC) filters	0.08 µg/sample[b]	NIOSH 2014b; Method 7304, Issue 1
Biological tissues (nail, liver, lungs, etc.)	6 µg/g[c]	NIOSH 2018; Method 8200, Issue 1
Water, wastewater, and solid wastes	5.4 mg/L[d]	EPA 1994a; Method 200.7
Drinking water	0.2 µg/L[e]	EPA 2003; Method 200.5
Groundwaters, surface waters, and drinking water	0.01–0.5 µg/L 0.2 mg/kg[f]	EPA 1994b; Method 200.8
Groundwater, surface water, drinking water, storm runoff, industrial and domestic wastewater	0.7 µg/L[g]	EPA 1994c; Method 200.9
Air	0.00001 µg/L[h]	EPA 2020a
Food	6.02 µg/kg[f]	FDA 2020
Serum	2.5 µg/dL[i]	CDC 2018

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Inductively coupled argon plasma-atomic emission spectroscopy.
[c]Inductively coupled plasma-atomic emission spectroscopy.
[d]Inductively coupled plasma-atomic emission spectrometry.
[e]Axially viewed inductively coupled plasma-atomic emission spectrometry.
[f]Inductively coupled plasma-mass spectrometry.
[g]Graphite furnace atomic absorption.
[h]Inductively coupled plasma-mass spectrometry or x-ray fluorescence.
[i]Inductively coupled plasma dynamic reaction cell mass spectrometry.

Table 5-10. Summary of Environmental Levels of Copper

Media	Low	High	For more information
Outdoor air (ppbv)	0.002	5.14	Table 5-13 or Section 5.5.1
Indoor air (ppbv)	0.008	0.012	Section 5.5.1
Surface water (ppb)	1	123,000	Tables 5-14 and 5-16 or Section 5.5.2
Groundwater (ppb)	<1	520,000	Tables 5-14 and 5-16 or Section 5.5.2
Drinking water (ppb)	<5	10,200	Table 5-15 or Section 5.5.2
Food (ppb)	0	135	Table 5-22 or Section 5.5.4
Soil and sediments (ppb)	0.001	310,000,000	Section 5.5.3
Biota (ppb)	0	171,000	Section 5.5.4

Detections of copper in air, water, and soil at NPL sites are summarized in Table 5-11.

Table 5-11. Copper Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	235	368	16.2	360	197
Soil (ppb)	411,000	435,000	17.1	468	250
Air (ppbv)	0.113	0.332	80.5	28	20

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Human exposure to copper in air comes from both natural and anthropogenic sources. The concentrations of copper in air can be higher in the proximity of major sources such as smelters, mining operations, and combustion sources (e.g., power plants, incinerators, automobiles, etc.). Yearly mean data from EPA's Air Quality System (AQS) for the years 2012–2022 are reported in Table 5-12. The AQS database contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. Most monitoring sites reporting sampling for copper were located in California and a few others have been located in Michigan in some years (including three in 2016, six in 2017, two in 2018, and two in 2019). Based on the most up-to-date data in Table 5-12 (2020–2022), in areas where copper is present in ambient air, the general population is expected to be exposed to average copper concentrations in air of ≤0.0238 μg/m^3 and maximum concentrations of ≤0.160 μg/m^3

Table 5-12. Summary of Annual Concentration of Copper (µg/m^3) Measured in Ambient Air Samples at Locations Across the United States[a]

Year	Number of monitoring locations	Number of samples	Average of the arithmetic mean at all locations	Maximum concentration
2022[b]	10	63	0.0219	0.0640
2021	13	331	0.0182	0.1600
2020	13	212	0.0238	0.0745
2019	8	353	0.0255	0.3970
2018	13	495	0.0283	0.4090
2017	14	578	0.0964	3.4400
2016	2	107	0.0363	0.4020
2015	25	785	0.1476	4.1400
2014	25	1,226	0.1109	3.6100
2013	28	1,400	0.1265	3.8400
2012	28	1,479	0.9019	1.8500

[a]24-hour sampling period.
[b]As of October 24, 2022.

Source: EPA Air Quality System (AQS) annual summaries (EPA 2022a)

One study found that the mean concentration of copper in ambient air from 13 U.S. cities was 0.005 µg/m^3; concentrations ranged from 0.002 to 0.006 µg/m^3 (Chen and Lippmann 2009). The results of several studies in which concentrations of copper in air were reported are described below and summarized in Table 5-13. It should be noted that older data may not be representative of current concentrations, given the reduction of ambient air pollution in the United States.

Table 5-13. Outdoor Air Monitoring Data for Copper

Location(s)	Geographic type	Date(s)	Mean concentration (ng/m^3)	Notes	Reference
United States	Urban	1977	207.5	4,648 samples[a]	EPA 1984
United States	Urban	1978	200.8	3,615 samples[a]	
United States	Urban	1979	259.3	2,507 samples[a]	
United States	Nonurban	1977	193.2	709 samples[a]	
United States	Nonurban	1978	265.7	458 samples[a]	
United States	Nonurban	1979	141.7	235 samples[a]	
Smokey Mountain National Park	Remote	1979	1.6	Above canopy, crustal enrichment factor 31	Davidson et al. 1985
Olympic National Park	Remote	1980	5.6	Crustal enrichment factor 76	

Table 5-13. Outdoor Air Monitoring Data for Copper

Location(s)	Geographic type	Date(s)	Mean concentration (ng/m^3)	Notes	Reference
Camden, New Jersey	Urban	Summer 1981 and 1982	16.0–18.0[b]		Lioy et al. 1987
Elizabeth, New Jersey	Urban	Summer 1981 and 1982	21.0–29.0[b]		
Newark, New Jersey	Urban	Summer 1981 and 1982	25.0–33.0[b]		
Ringwood, New Jersey	Rural	Summer 1981 and 1982	13.0–63.0[b]		
Camden, New Jersey	Urban	Winter 1982 and 1983	17.0–21.0[b]		
Elizabeth, New Jersey	Urban	Winter 1982 and 1983	28.0–36.0[b]		
Newark, New Jersey	Urban	Winter 1982 and 1983	21.0–27.0[b]		
Ringwood, New Jersey	Rural	Winter 1982 and 1983	6.0–18.0[b]		

[a]Samples from National Survey.
[b]Concentrations reported by Lioy et al. (1987) are geometric means.

Davies and Bennett (1985) reported average atmospheric copper concentrations of 5–50 ng/m^3 in rural areas and 20–200 ng/m^3 in urban locations. 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^3 (Schroeder et al. 1987). Remote and rural areas have concentrations of 0.029–12 and 3–280 ng/m^3, respectively (Schroeder et al. 1987). In remote areas such as national parks, differences in copper concentrations have been attributed to greater vegetative cover and higher moisture and larger amounts of exposed rock and soil (Davidson et al. 1985). Copper follows the same pattern as other heavy metals, in that increased copper levels are present in urban areas in winter and in rural areas in summer (Evans et al. 1984; Lioy et al. 1987.

Anderson et al. (1988) performed a study of the atmospheric aerosols collected at a site in Chandler, Arizona. Several major copper smelters are located ~120 km to the southeast, which were upwind of the sampling site during approximately 50% of the study period. The most abundant type of copper-bearing particle, representing 74% of the total, was associated with sulfur. However, the analysis was not able to specify the form of sulfur present. Anderson et al. (1988) concluded that the smelters to the southeast were the probable source. Mine waste dump sites are another source of airborne copper (Mullins and

Norman 1994). Particle size distribution and the concentration of copper in particle size ranges differ depending on the mine waste site (Mullins and Norman 1994).

Mean concentration ranges of copper in remote (any area of lowest copper concentration such as the Antarctic or Arctic) and rural (any site that represents a regional background that is not directly influenced by local anthropogenic emissions) precipitation ranges were 0.013–1.83 and 0.68–1.5 ppb, respectively, based on a weight per unit volume basis (Barrie et al. 1987). Although an earlier survey referred to by these investigators (Galloway et al. 1982) yielded much higher values of 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 ppb during 1982 (Chan et al. 1986). These concentrations showed little spatial variability. Concentration of copper in cloud water over Olympic Peninsula in Washington State has been measured at 1.7±1.6 µg/L (air equivalent mean concentration of 0.5 ng/m^3) (Vong et al. 1997). Copper concentrations in precipitation may be affected by proximity to industry, but concentrations do not appear to be affected by proximity to automobile emissions. Elevated levels of copper in fog water were observed 3 km downwind from a refuse incinerator in Switzerland (Johnson et al. 1987). The concentration of copper in rain samples taken within 2–15 km downwind of the Claremont, New Hampshire municipal waste incinerator was 0.11–2.12 µg/L, with a mean concentration of 0.87 µg/L (Feng et al. 2000). Cu(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. The highest values were recorded just as the fog was dissipating.

Copper deposition from automobile emissions, as measured by the concentration of copper in snow, did not vary significantly as a function of distance (15–150 m) from an expressway in Montreal, Canada (Loranger et al. 1996).

Airborne concentrations of copper in the indoor atmosphere within homes located in Suffolk and Onondaga counties in New York average between 8 and 12 ng/m^3 (Koutrakis et al. 1992). The concentration was significantly affected by the use of kerosene heaters, which were found to emit copper into the indoor air at a rate of 15,630 ng/hour (Koutrakis et al. 1992).

5.5.2 Water

Copper is widely distributed in water since it is a naturally occurring element. The results of several studies in which concentrations of copper in water were reported are described below and summarized in

Tables 5-14, 5-15, and 5-16. Data from older studies may have been analyzed with instrumentation with high detection limits, and samples were often contaminated during collection, treatment, and analysis.

Table 5-14. Surface Water and Groundwater Monitoring Data for Copper

Location(s)	Type	Date(s)	Range (µg/L)[a]	Mean concentration (µg/L)	Notes	Reference
Surface water						
United States	USGS survey stations	Not specified	Not reported	4.2	53,862 occurrences	Eckel and Jacob 1988
New Jersey	Representative sample	1977–1979	Maximum 261.0	Not reported	1,603 samples taken from 600 sites; median of 3.0	Page 1981
East Arctic Ocean	Ocean water	1980	32–489 ng/kg	93±38 ng/kg	26 locations 0.5–1 m depth; mean concentration at depth was 400 ng/kg; unfiltered samples	Mart et al. 1984
Atlantic Ocean	Ocean water	Not specified	0.79–3.9 nM	Not reported	20 sites, 2 cruises, 0–1 m depth; unfiltered samples	Yeats 1988
Massachusetts	Pond water	April 1971–March 1972	<10–105	Not reported	Low in summer, high in winter	Kimball 1973
Canada	Lake water	November 1976–January 1977	1–8	2	Acid sensitive lakes	Reed and Henningson 1984
Lake Superior	Lake water	August–September 1991	629–834	756	3 samples; filtered samples	Nriagu et al. 1996
Lake Erie	Lake water	August 1993	703–1,061	870	9 samples; filtered samples	Nriagu et al. 1996
Lake Ontario	Lake water	May–June 1993; October 1993	540–1,098	830	14 samples; filtered samples	Nriagu et al. 1996
Indiana	Stream and pond water, near acidic mine drainage		32–1,200	736	12 samples taken from streams and ponds near abandoned Cerbat Mountain coal mines; filtered samples	Allen et al. 1996

Table 5-14. Surface Water and Groundwater Monitoring Data for Copper

Location(s)	Type	Date(s)	Range (µg/L)[a]	Mean concentration (µg/L)	Notes	Reference
Cerbat Mountains, northwestern Arizona	Surface water in a copper mining area	March 1995, September 1995	100–69,000	Not reported	Samples obtained from the Cerbat Mountains mining area; 15 surface water sites with 14 sites downstream from old tailings and adits; median of 1,200	Rösner 1998
Groundwater						
New Jersey	Representative sample	1977–1979	Maximum 2,783.0	5.0	1,063 samples, 90th percentile 64.0 ppb, groundwater may or may not be used for drinking water	Page 1981
Denver, Colorado	Shallow monitoring well	1993	<1–14	2.0	30 monitoring wells, 22 with PVC casings and 8 with metal casings; samples obtained after purging well 20 minutes; filtered pesticide samples and unfiltered VOC samples	Bruce and McMahon 1996

[a]Range is µg/L unless otherwise stated

USGS = United States Geological Survey; PVC = polyvinyl chloride; VOC = volatile organic compound

Table 5-15. Copper Concentrations in Drinking Water Monitoring Data

Location(s)	Type	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Nova Scotia, four communities	Running tap water from private wells	NS	40–200	NR	53% of homes exceeded Canada's maximum permissible limit for copper (1.0 mg/L)	Maessen et al. 1985
	Standing tap water from private wells	NS	130–2,450	NR		
New Bedford, Massachusetts	Running tap water from private wells	April 1987, 1992, 1993 July 1992	NR	230–560	24 sample areas included	Yannoni and Piorkowski 1995

Table 5-15. Copper Concentrations in Drinking Water Monitoring Data

Location(s)	Type	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Canada (National Survey)	Raw, treated, and distributed water	November 1976–January 1977	≤5.0–620	NR	Sampled raw, treated, and distributed water from 70 municipalities; median concentration was 20; noted differences based on source and type of water; filtered samples	Meranger et al. 1979
New Jersey	School drinking water	1991–1992	BD (50) – 10,200	NR	Sampled two water fountains in each of 50 schools. Median concentration ranged from 68 to 260 µg/L depending on time of day; noted differences based on time of day and corrosivity of samples	Murphy 1993
California	School drinking water	2017–2022	1,302–2,140	224 (first draw); 158 (second draw)	Three (4%) school drinking fountains had copper levels that exceeded the EPA action level (1.3 mg/L) on the first draw; the three schools had a greater proportion of students eligible for free/reduced priced meals compared to the average California public school	Garvey et al. 2023
Michigan, Massachusetts, Maryland, Virginia	Public schools and childcare facilities drinking water	2016–2020	Range of maximum values: 7,730–53,200	NR	Samples from 133 schools in Michigan; 84,153 water fixtures in 2,000 schools and childcare facilities in Massachusetts: 40 schools in Maryland; and 25 schools in Virginia	Montagnino 2022
Berlin, Germany	Running tap water from municipal water supply	June 1998–March 2001	9–4,200	436–561	2,619 samples from 2,944 households	Zietz et al. 2003a

Table 5-15. Copper Concentrations in Drinking Water Monitoring Data

Location(s)	Type	Date(s)	Range (µg/L)	Mean (µg/L)	Notes	Reference
Lower Saxony, Germany	Tap water from municipal water supply	January 1997–November 1999	>10–6,400	106–183	1,619 stagnated water samples and 1,660 random daytime samples	Zietz et al. 2003b

BD = below detection; EPA = U.S. Environmental Protection Agency; NR = not reported

Table 5-16. Summary of Concentrations of Copper (µg/L) Measured in Surface and Groundwater Samples Across the United States

Year range	Average	Maximum concentration	Number of samples[a]	Percent detected
Surface water				
2020–2022[b]	21.9	25,490	33,645	74%
2015–2019	47.8	23,600	90,360	78%
2010–2014	83.7	123,000	62,180	71%
Groundwater				
2020–2022[a]	31.5	10,400	2,309	68%
2015–2019	41.7	43,000	6,672	76%
2010–2014	279.3	520,000	7,711	79%

[a]Samples collected from the U.S. Geological Survey S Water Science Center monitoring sites and other state environmental departments in over 37 U.S. states.
[b]As of October 24, 2022.

Source: WQP 2022

Groundwater collected from wells from 2013 to 2016 by USGS for the National Water-Quality Assessment Project show copper concentrations of 0.2–98.4 µg/L (USGS 2020b). Copper concentrations in drinking water can vary widely (≤5–53,200 ppb) and can exceed the action level of 1,300 ppb (1.3 mg/L) that is the regulatory Maximum Contaminant Level Goal (MCLG) for copper in drinking water (EPA 1991, 2021b). Copper was found at concentrations greater than EPA's Treatment Technology Action Level of 1.3 mg/L in 0.06% of domestic wells sampled by USGS from 1991 to 2004 (USGS 2009b). An action level is the concentration of a contaminant in potable water, which, if exceeded in 10% of monitoring systems, requires treatment for corrosion control and public notification (EPA 2018b).

A national water quality study was done for contaminants including copper over the period of 1991–2010 (USGS 2014). The study evaluated frequency of copper concentrations greater than the human-health benchmark of 1,300 µg/L (1.3 mg/L) and concentrations outside of recommended non-health guidelines for drinking water in principal aquifers in the United States. For the 37 aquifers used for drinking water and sampled for copper, the percentage of all samples containing copper at ≥1.3 mg/L was 0.03%. For the 17 shallow groundwater aquifers beneath agricultural land and 21 shallow groundwater aquifers beneath urban land, 0% of samples contained copper at ≥1.3 mg/L (USGS 2014).

Elevated concentrations of copper in drinking water can result from leaching processes from source materials such as piping, tanks, and valves in water distribution systems. Copper in tap water is related to Cu(II) mineralogy and solubility, which have been shown to be affected by age, pH, and dissolved inorganic carbon within the system (Montagnino et al. 2022). Data from 208 U.S. households indicates that about a third of U.S. homes have drinking water containing more than 0.1 ppm copper (Brewer 2010). 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 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 standing water was variable and exceeded 1.0 ppm in 53% of the homes. 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). In a review of copper in drinking water at schools (n=12,193) and childcare centers (n=5,460) using public water systems as of July 2020, it was estimated that a total of 6,419 (13.2%) copper action level exceedances were reported since 1992. Voluntary testing for copper in drinking water conducted in 2016 at 133 schools in Michigan, ~2,000 schools in Massachusetts, and 40 schools in Maryland found that 11, 351, and 4 schools/childcare

facilities, respectively, had copper levels above the EPA action limit. The maximum levels of copper found were 15.5 mg/L (15.5 ppm) in Detroit at a kitchen faucet, 10.2 mg/L (10.2 ppm) in Maryland at a kitchen sink, and 53.2 mg/L (53.2 ppm) in Massachusetts at a kitchen faucet. In 2019 and 2020, voluntary testing in Virginia identified nine and six instances, respectively, of public school exceedances, with maximum values reported at a kitchen sink of 7.73 mg/L (7.73 ppm) in 2019 and 11.4 mg/L (11.4 ppm) in 2020 (Montagnino et al. 2022).

In homes with copper piping, the mean concentration of copper in tap water has been shown to decline with the age of the home. In a sampling of tap water of 2,619 households in Berlin, Germany that are supplied with municipal drinking water, the mean concentration of copper decreased from 0.77 ppm in homes with stated ages of 0–<5 years to 0.23 ppm in homes with stated ages of 35–<40 years (Zietz et al. 2003a). In another study of 1,619 homes in Lower Saxony, Germany, the mean concentration of copper in first draw tap water decreased from 0.37 ppm in homes with stated ages of 0–<5 years to 0.05 ppm in homes with stated ages of 35–<45 years (Zietz et al. 2003b). These decreases of copper concentration with age were attributed to a buildup of a surface layer on the piping that reduced corrosion. However, in these same two studies, it was found that the concentration of copper in tap water began to increase with increasing age in homes with stated ages of >45 years. This increase in copper concentration was attributed to the increased probability of repair or partial placement (or unknown total replacement) of piping in these homes.

In a study of 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 90th 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 suggests that the sources of contamination of surface water and groundwater are different. The nature of the sites with elevated levels of copper was not indicated.

Several studies reported copper levels in surface water with a range of 0.5–1,000 ppb and a median of 10 ppb; seawater contained <1–5 ppb (EPA 1980b; Davies and Bennett 1985; Mart et al. 1984; Page 1981; Yeats 1988). The geometric mean, standard deviation, and median concentration of dissolved copper in surface water based on 53,862 occurrences in the Water Quality Portal (WQP) are 4.2±2.71 and 4.0 ppb, respectively (WQP 2020). Higher concentrations tend to be found in New England, the western Gulf, and the lower Colorado River.

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 from tailings and acid mine drainage from gold mining operations in the Black Hills of South Dakota. Copper 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 mg/kg (May et al. 2001).

In a survey of sources of copper in stormwater, measurements of copper concentrations in stormwater 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; however, they were much higher in unfiltered samples (copper bound to particulate matter) with mean values (in µg/L) of 280 (street runoff), 135 (vehicle service areas), 116 (parking areas), 110 (roof areas), 81 (landscaped areas), 50 (urban creeks), and 43 (retention ponds) (Pitt et al. 1995).

As a result of improvements in controlling the quality of discharges from municipal and industrial wastewater 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).

The copper concentration in some bodies of water evidently varies with season. In a study of a small pond in Massachusetts from April of 1971 to March 1972, the concentration of copper was found to vary, decreasing during the spring and early summer to lows of <10–30 ppm in early August and then increasing when the pond was under the cover of ice to maximum values of 80–105 ppb in late January and early February (Kimball 1973). Similar seasonal variations were noted in the epilimnion of the offshore waters of the Great Lakes (Nriagu et al. 1996). In both examples, the cycling of copper concentrations is thought to be a response to biological need and copper uptake during the growing season and its subsequent release from seasonal die-off and decay of biota.

Copper concentrations in seawater usually are in the 1–5 ppb range (EPA 1980b). Copper levels are overall lower in the Pacific Ocean versus the Atlantic Ocean and higher near the continental shelf than in the open ocean. Copper concentrations in surface water at a depth of 1 m 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 sampled at a depth of 1 m of the eastern Arctic Ocean was 93 ppt (Mart et al.

1984). As noted in a review by Kennish (1998), concentrations of copper in estuarine and coastal waters in the United States were 0.3–3.8 and 0.1–2.5 ppb, respectively.

5.5.3 Sediment and Soil

Copper occurs naturally in the Earth's crust at a mean concentration of approximately 50 ppm (Henckens and Worrell 2020). Rauch and Graedel (2007) estimated that 9.9 $x10^{11}$ Gg (9.9$x10^{8}$ kg) of copper exists in the Earth's crust. Several databases report copper levels in soil and sediment in the United States. The National Geochemical Database by USGS (2016) reported that copper occurs in soils at levels of 0.005–200,000 ppm and in sediment at levels of 0.001–150,000 ppm. The median level of copper in soils and sediments reported to the National Geochemical Database was 30 ppm in soils and sediments (USGS 2016). The National Water Information System by USGS reported copper in soil at levels of 0.84–9.8 mg/kg (WQP 2020). Copper occurs in sediments at levels of 0.12–35,700 mg/kg (WQP 2020). EPA reported levels in soil of 0.58–334 mg/kg (WQP 2020). In 2007, USGS conducted a geochemical and mineralogical survey of soils of the conterminous United States. The mean concentration of copper calculated from the 4,841 samples taken was 17.9 mg/kg, with values ranging from <0.5 to 996 mg/kg (USGS 2013). Data as of October 2022 from USGS monitoring systems across the United States are reported in Tables 5-17, 5-18, and 5-19 (WQP 2022).

Table 5-17. Summary of Concentrations of Copper (µg/kg) Measured in Soil Samples at Superfund Sites

Year range	Average	Maximum concentration	Number of samples	Percent detected
2020–2022[a]	–	–	–	–
2015–2019	–	–	–	–
River Mile 11 East Supplemental Remedial Investigation/Feasibility Study, Portland Harbor Superfund Site, Oregon				
2010–2014	48,994	146,000	17	100%

[a]As of October 24, 2022.

Source: WQP 2022

Table 5-18. Summary of Concentrations of Copper (ppb) Measured in Soil Samples Across the United States

Year range	Average	Maximum concentration	Number of samples	Percent detected
2020–2022[a]	2,545,044	82,500,000	76[b]	100%
2015–2019	168,933	3,830,000	1,463[c]	78%
2010–2014	387,270	310,000,000	3,542[d]	61%

[a]As of October 24, 2022.
[b]Samples collected from monitoring sites in Arizona, Kansas, South Dakota, and Wisconsin.
[c]Samples collected from monitoring sites in Louisiana, Montana, New York, North Carolina, South Dakota, Texas, and Virginia.
[d]Samples collected from monitoring sites in Alabama, Alaska, Arizona, Florida, Hawaii, Montana, New Mexico, Oklahoma, South Dakota, Texas, Utah, and Wisconsin.

Source: WQP 2022

Table 5-19. Summary of Concentrations of Copper (ppb) Measured in Sediment Samples Across the United States

Year range	Average	Maximum concentration	Number of samples	Percent detected
2020–2022[a]	396,843	160,000,000	990[b]	87%
2015–2019	114,339	42,200,000	10,801[c]	89%
2010–2014	85,326	17,500,000	15,305[d]	92%

[a]As of October 24, 2022.
[b]Samples collected from monitoring sites in Alabama, Arizona, Florida, Hawaii, Illinois, Mississippi, Montana, New Jersey, Texas, and Wisconsin.
[c]Samples collected from monitoring sites in over 27 U.S. States.
[d]Samples collected from monitoring sites in over 36 U.S. States.

Source: WQP 2022

Anthropogenic and industrial sources can contribute to copper concentrations in soils (Bassetti et al. 2023). Copper concentrations in soil may be much higher in the vicinity of a source of copper emissions, such as a mining operation or smelter activity. Concentrations in the top 5 cm of soil near the boundary of a secondary copper smelter were 2,480±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). The observation that the copper concentrations were highest in soils within 1–2 km from the smelter and decreased exponentially with increasing distance from the plant suggests that copper in the soil from the study area was primarily derived from particulate emissions from the smelter. In urban surface soils used for community gardens in Pennsylvania, concentrations of copper were greater in

areas where smelting activities were identified as a contamination source (59.4–388.8 mg/kg) compared to areas with anthropogenic source contamination (11.6–110.1 mg/kg) (Bassetti et al. 2023).

In 2021, elemental copper concentrations were measured in urban forest soils at 460 locations in Hartford, Connecticut (n=140), Lexington, Massachusetts (n=152), and Springfield, Massachusetts (n=168), which represent multiple land uses including single-family residential, multi-family residential, commercial, industrial, education, lands, and parks (including vacant lots), and all other or unknown land uses. The study reported mean copper concentrations of 17–35 mg/kg (maximum, 106.8–117.2 mg/kg) and there were no significant differences for copper among the land uses evaluated (Sirkovich et al. 2023). Soil samples collected from August to September 2021 in Grand Forks, North Dakota, characterized as poorly drained clay and silt with relatively low permeability, had measured concentrations of copper of 12.58–21.84 mg/kg in park soils and 13.17–22.53 mg/kg in residential soils (Saleem et al. 2023).

From an analysis of the spatial distribution of the copper concentrations in soils where lowest copper soil concentrations are observed for rural (agricultural) soils and highest in soils obtained from industrialized urban areas, it was concluded that most of the contamination was a result of airborne deposition from industrial sources. Concentrations of copper were 16.9–171 mg/kg in soil samples from urban gardens in New York and 19.7–62.8 mg/kg in soil samples from an orchard (Cai et al. 2016). At an abandoned wood impregnation site in Denmark, copper concentrations of 1,300 mg/kg dry weight were measured in CCA-polluted soils in March of 2020 (Tang et al. 2023).

The concentrations of copper in soils and sediments were assessed as part of the National Water-Quality Assessment Program (Rice 1999). The median concentrations of copper at 541 sites throughout the conterminous United States were 5–70 µg/g (dry weight). At nonurban indicator sites, the median concentrations were 13–47 µg/g. The same study derived an average crustal abundance of copper of 60 µg/g (60 ppm).

Sediment is an important sink and reservoir for copper. 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 mg/kg dry weight, over 100 times the concentration in a baseline lake 180 km away.

An analysis of the Coastal Sediment Database (COSED) showed that 73% of coastal waterways had copper concentrations <42 µg/g; 25% had copper concentrations between 42 and 210 µg/g; and 2% were >210 µg/g. These higher concentrations were 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 (151 ppm) have been measured in sediments to depths of 54 cm (Bopp et al. 1993). Combined sewer outflows can also contribute significantly to the copper content of 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 mg/kg, with a concentration of 151 ppm in sediment core samples obtained at a depth of 52–54 cm (Bopp et al. 1993). The highest concentrations were found in the middle depths (16–44 cm), ranging from 280 to 406 mg/kg during a period when untreated industrial effluents and sewage outflows entered the bay. However, copper concentrations in surface sediments (0–2 cm) were measured at 208 mg/kg. The decrease in copper concentration in the surface sediments suggests that efforts to reduce metal contaminants from sewage outflows have been making an impact on the copper concentrations in receiving waters and their sediments.

5.5.4 Other Media

In addition to the ingestion of drinking water, the consumption of food is the other primary route for copper intake in the general population. Copper is an essential nutrient present in many plant and animal foods and available as a dietary supplement. The RDAs and Tolerable Upper Intake Levels (ULs) by life stage group are presented in Table 5-20. Copper intake per day based on NHANES data is provided in Table 5-21. Voluntary food fortification in the United States increases the probability of consuming copper and has been associated with copper intakes exceeding the UL for children ages 1–3 years (Sacco et al. 2013).

Table 5-20. Dietary Reference Intakes for Copper

Life stage group[a]	RDA (µg/day)	UL (µg/day)
1–3 years	340	1,000
4–8 years	440	3,000
9–13 years	700	5,000
14–18 years	890	8,000
≥19 years	900	10,000

Table 5-20. Dietary Reference Intakes for Copper

Life stage group[a]	RDA (µg/day)	UL (µg/day)
Pregnant females, ≤18 years	1,000	8,000
Pregnant females, 19–50 years	1,000	10,000
Lactating females, ≤18 years	1,300	8,000
Lactating females, 19–50 years	1,300	10,000

[a]RDAs are not estimated for ages 0–12 months. Adequate intake at this life stage is 220 µg/day.

RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level

Source: IOM 2006

Table 5-21. Mean Amount of Copper Consumed per Individual by Gender and Age

Gender and age (years)	Amount consumed (mg)	Standard error
Males		
2–5	0.8	0.02
6–11	0.9	0.05
12–19	1.1	0.03
20–29	1.2	0.05
30–39	1.4	0.06
40–49	1.4	0.07
50–59	1.5	0.07
60–69	1.3	0.05
≥70	1.3	0.05
Females		
2–5	0.7	0.02
6–11	0.9	0.03
12–19	0.9	0.04
20–29	1.1	0.04
30–39	1.1	0.04
40–49	1.0	0.03
50–59	1.1	0.06
60–69	1.2	0.05
≥70	1.1	0.03

Source: USDA 2020

The FDA Total Diet Survey provides copper concentration in various foods, examples of which are given in Table 5-22 (FDA 2017). The copper content in baby food is given in Table 5-23. The highest concentrations of dietary copper were found in liver; some oat and bran cereals; some legumes and nuts;

and chocolate syrup, candy, and some desserts. Coleman et al. (1992) reported copper concentrations in the edible tissues of livestock and poultry with the highest mean concentrations (mg/kg) found in liver (cow 3.7; 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).

Table 5-22. Copper Content of Selected Foods (mg/kg)

Food description	Mean±SD	Food description	Mean±SD
Liver (beef/calf), pan-cooked with oil	135.00±40.78	Pear, canned in light syrup	0.55±0.22
Sunflower seeds (shelled), roasted, salted	19.23±0.40	Pepper, sweet, green, raw	0.55±0.28
Walnuts, shelled	11.70±0.00	Beef with vegetables in sauce, from Chinese carry-out	0.54±0.24
Peanut butter, creamy	4.94±0.38	Cornbread, homemade	0.54±0.03
Peanuts, dry roasted, salted	4.82±0.16	Meatloaf, beef, homemade	0.54±0.08
Raisin bran cereal	4.32±0.31	Pie, pumpkin, fresh/frozen	0.54±0.04
Syrup, chocolate	3.82±0.26	Salmon, steaks/fillets, baked	0.53±0.12
Candy bar, milk chocolate, plain	3.67±0.33	Cream of wheat (farina), enriched, cooked	0.52±0.17
Shredded wheat cereal	3.66±0.38	Tomato, raw	0.52±0.22
Potato chips	3.57±0.35	Chicken potpie, frozen, heated	0.51±0.03
Oat ring cereal	3.55±0.23	Corn flakes cereal	0.51±0.04
Brownie	3.43±0.17	Frankfurter (beef/pork), boiled	0.51±0.08
Raisins	3.30±0.35	Tomato juice, bottled	0.51±0.06
Pinto beans, dry, boiled	3.18±0.39	Chicken breast, fried, fast-food (with skin)	0.50±0.07
Avocado, raw	2.96±0.59	Pineapple, canned in juice	0.50±0.05
Granola with raisins	2.90±0.38	Chicken nuggets, fast-food	0.49±0.10
Bread, whole wheat	2.77±0.02	Pie, apple, fresh/frozen	0.48±0.07
White beans, dry, boiled	2.71±0.58	Pineapple juice, frozen concentrate, reconstituted	0.48±0.05
Chocolate chip cookies	2.70±0.70	Collards, fresh/frozen, boiled	0.47±0.06
Bread, multigrain	2.64±0.16	Potatoes, mashed, prepared from fresh	0.47±0.23
Granola bar, with raisins	2.47±0.85	Orange juice, frozen concentrate, reconstituted	0.46±0.06
Cake, chocolate with icing	2.38±0.17	Blueberries, raw	0.45±0.00
Mushrooms, raw	2.34±0.50	Tuna, canned in water, drained	0.45±0.05
Sweet potato, baked, peel removed	2.31±0.00	Beets, canned	0.44±0.12
Candy bar, chocolate, nougat, and nuts	2.25±0.11	Brussels sprouts, fresh/frozen, boiled	0.43±0.04
Popcorn, microwave, butter-flavored	2.23±0.21	Fruit cocktail, canned in light syrup	0.43±0.02
Pork and beans, canned	2.10±0.14	Watermelon, raw/frozen	0.43±0.33
Lima beans, immature, frozen, boiled	2.08±0.20	Orange (navel/Valencia), raw	0.42±0.07

Table 5-22. Copper Content of Selected Foods (mg/kg)

Food description	Mean±SD	Food description	Mean±SD
Sandwich cookies with filling	2.06±0.42	Orange juice, bottled/carton	0.42±0.02
Ice cream, chocolate	1.85±0.00	Strawberries, raw/frozen	0.40±0.13
Refried beans, canned	1.85±0.13	Turkey breast, oven-roasted	0.40±0.07
Crisped rice cereal	1.82±0.14	Peach, canned in light/medium syrup	0.39±0.03
Crackers, graham	1.79±0.20	Carrot, fresh, peeled, boiled	0.36±0.09
Meal replacement, liquid RTD, any flavor	1.70±0.62	Green beans, canned	0.36±0.08
Pretzels, hard, salted	1.66±0.15	Onion, mature, raw	0.36±0.06
Black olives	1.63±0.37	Soup, tomato, canned, condensed, prepared with water	0.36±0.03
Tomato catsup	1.55±0.17	Chicken breast, oven-roasted (skin removed)	0.35±0.05
Rice, brown, cooked	1.52±0.00	Eggplant, fresh, peeled, boiled	0.34±0.25
Chili con carne with beans, canned	1.51±0.03	Applesauce, bottled	0.33±0.06
Lamb chop, pan-cooked with oil	1.51±0.10	Bologna (beef/pork)	0.33±0.02
Bagel, plain, toasted	1.48±0.14	Cantaloupe, raw/frozen	0.33±0.22
Bread, rye	1.46±0.29	Cheese, Swiss, natural	0.33±0.05
French fries, fast-food	1.43±0.33	Corn, fresh/frozen, boiled	0.33±0.24
Shrimp, boiled	1.40±0.56	Grapefruit, raw	0.33±0.04
Crackers, saltine	1.38±0.14	Carrot, baby, raw	0.32±0.23
English muffin, plain, toasted	1.35±0.14	Apricots, canned in heavy/light syrup	0.30±0.06
Noodles, egg, enriched, boiled	1.34±0.29	Soup, vegetable beef, canned, condensed, prepared with water	0.30±0.06
Soup, bean with bacon/pork, canned, condensed, prepared with water	1.28±0.02	Broccoli, fresh/frozen, boiled	0.29±0.22
Spaghetti, enriched, boiled	1.25±0.34	Dill cucumber pickles	0.27±0.03
Bread, white, enriched	1.23±0.16	Grapefruit juice, bottled	0.27±0.06
Beef steak, loin/sirloin, broiled	1.18±0.46	Cod, baked	0.26±0.00
Pineapple, raw/frozen	1.16±0.00	Sweet & sour sauce	0.26±0.23
Spaghetti with meat sauce, homemade	1.16±0.10	Cheese, cheddar, natural (sharp/mild)	0.25±0.18
Bread, white roll/bun (hamburger/hotdog)	1.15±0.00	Lettuce, leaf, raw	0.23±0.46
Beef stroganoff with noodles, homemade	1.14±0.25	Milk, chocolate, low-fat, fluid	0.21±0.14
Fruit-flavored cereal, presweetened	1.13±0.20	Grape juice, frozen concentrate, reconstituted	0.20±0.03
Crackers, butter-type	1.12±0.11	Prune juice, bottled	0.20±0.01
Burrito with beef, beans, and cheese, from Mexican carry-out	1.11±0.21	Cucumber, peeled, raw	0.16±0.18
Pizza, cheese, fast-food	1.11±0.00	Cake, yellow with icing	0.15±0.17

Table 5-22. Copper Content of Selected Foods (mg/kg)

Food description	Mean±SD	Food description	Mean±SD
Quarter-pound hamburger on bun, fast-food	1.09±0.04	Cream substitute, non-dairy, liquid/frozen	0.13±0.23
Tortilla, flour	1.08±0.11	Wine, dry table, red/white	0.12±0.04
Turkey, ground, pan-cooked	1.08±0.00	Cheese, American, processed	0.11±0.20
Peas, green, fresh/frozen, boiled	1.05±0.19	Corn, canned	0.11±0.18
Pizza, cheese and pepperoni, regular crust, from pizza carry-out	1.03±0.05	Apple juice, bottled	0.10±0.03
Corn/tortilla chips	1.02±0.10	Sour cream dip, any flavor	0.10±0.17
Fried rice, meatless, from Chinese carry-out	1.02±0.18	Turnip, fresh/frozen, boiled	0.10±0.17
Quarter-pound cheeseburger on bun, fast-food	1.02±0.12	Catfish, pan-cooked with oil	0.09±0.18
Doughnut, cake-type, any flavor	1.00±0.28	Clam chowder, New England, canned, condensed, prepared with whole milk	0.09±0.15
Salami, luncheon-meat type (not hard)	0.96±0.12	Cottage cheese, creamed, low-fat (2% milk fat)	0.09±0.15
Asparagus, fresh/frozen, boiled	0.93±0.15	Luncheon meat (chicken/turkey)	0.09±0.16
Pork bacon, oven-cooked	0.93±0.22	Sorbet, fruit-flavored	0.09±0.15
Tortilla, corn	0.92±0.00	Soup, chicken noodle, canned, condensed, prepared with water	0.09±0.15
Potato, baked (with peel)	0.89±0.15	Lettuce, iceberg, raw	0.08±0.15
Banana, raw	0.87±0.15	Cabbage, fresh, boiled	0.07±0.14
Beef roast, chuck, oven-roasted	0.87±0.09	Fruit juice blend (100% juice), canned/bottled	0.05±0.05
Biscuits, refrigerated-type, baked	0.86±0.01	Cranberry juice cocktail, canned/bottled	0.03±0.05
Rice, white, enriched, cooked	0.85±0.15	Milk, low-fat (2%), fluid	0.03±0.04
Chicken leg, fried, fast-food (with skin)	0.84±0.12	Lemonade, frozen concentrate, reconstituted	0.02±0.04
Pork sausage (link/patty), oven-cooked	0.84±0.05	Tea, from tea bag	0.02±0.03
Sweet potatoes, canned	0.84±0.17	Milk, skim, fluid	0.01±0.03
Iced cinnamon roll	0.83±0.08	Milk, whole, fluid	0.01±0.03
Lasagna with meat, frozen, heated	0.83±0.07	Apple (red), raw (with peel)	0.00±0.00
Tomato sauce, plain, bottled	0.83±0.05	Beer	0.00±0.00
Fish sticks or patty, frozen, oven-cooked	0.82±0.19	Bottled drinking water (mineral/spring), not carbonated or flavored	0.00±0.00
Salami, dry/hard	0.82±0.00	Brown gravy, canned or bottled	0.00±0.00
Mustard, yellow, plain	0.81±0.06	Butter, regular (not low-fat), salted	0.00±0.00
Egg, cheese, and ham on English muffin, fast-food	0.80±0.13	Candy, hard, any flavor	0.00±0.00
Oatmeal, plain, cooked	0.77±0.20	Carbonated beverage, cola, low-calorie	0.00±0.00
Peach, raw/frozen	0.77±0.18	Carbonated beverage, cola, regular	0.00±0.00

Table 5-22. Copper Content of Selected Foods (mg/kg)

Food description	Mean±SD	Food description	Mean±SD
Tomato salsa, bottled	0.77±0.06	Carbonated beverage, fruit-flavored, regular	0.00±0.00
Chicken filet (broiled) sandwich on bun, fast-food	0.75±0.13	Cauliflower, fresh/frozen, boiled	0.00±0.00
Chicken leg, fried, fast-food (with skin)	0.75±0.00	Celery, raw	0.00±0.00
Macaroni salad, from grocery/deli	0.74±0.15	Cheese, Monterey jack	0.00±0.00
Biscuits, fast-food	0.73±0.00	Cheese, mozzarella	0.00±0.00
Potato salad, mayonnaise-type, from grocery/deli	0.71±0.27	Coffee, decaffeinated, from ground	0.00±0.00
Potato, boiled (without peel)	0.71±0.26	Coffee, from ground	0.00±0.00
Tuna noodle casserole, homemade	0.71±0.09	Coleslaw, mayonnaise-type, from grocery/deli	0.00±0.00
Chicken thigh, oven-roasted (skin removed)	0.70±0.15	Corn/hominy grits, enriched, cooked	0.00±0.00
Fish sandwich on bun, fast-food	0.69±0.06	Cream cheese	0.00±0.00
Okra, fresh/frozen, boiled	0.69±0.03	Cream, half & half	0.00±0.00
Taco/tostada with beef and cheese, from Mexican carry-out	0.69±0.08	Fruit drink (10% juice), canned or bottled	0.00±0.00
Pancakes, frozen, heated	0.68±0.05	Fruit drink, from powder	0.00±0.00
Pear, raw (with peel)	0.68±0.07	Gelatin dessert, any flavor	0.00±0.00
Breakfast tart/toaster pastry	0.67±0.08	Honey	0.00±0.00
Soup, Oriental noodles (ramen noodles), prepared with water	0.67±0.04	Ice cream, light, vanilla	0.00±0.00
Squash, winter (Hubbard or acorn), fresh/frozen, boiled	0.67±0.15	Ice cream, regular (not low-fat), vanilla	0.00±0.00
Beef, ground, regular, pan-cooked	0.66±0.09	Jelly, any flavor	0.00±0.00
Pork roast, loin, oven-roasted	0.64±0.02	Margarine, regular (not low-fat), salted	0.00±0.00
Eggs, boiled	0.63±0.18	Mayonnaise, regular, bottled	0.00±0.00
Eggs, scrambled with oil	0.63±0.10	Milk shake, vanilla, fast-food	0.00±0.00
Pork chop, pan-cooked with oil	0.62±0.06	Olive oil	0.00±0.00
Sugar cookies	0.62±0.06	Popsicle, fruit-flavored	0.00±0.00
Summer squash, fresh/frozen, boiled	0.62±0.23	Pudding, ready-to-eat, flavor other than chocolate	0.00±0.00
Grapes (red/green), raw	0.60±0.13	Salad dressing, creamy/buttermilk type, low-calorie	0.00±0.00
Green beans, fresh/frozen, boiled	0.60±0.18	Salad dressing, creamy/buttermilk type, regular	0.00±0.00
Spinach, fresh/frozen, boiled	0.60±0.14	Salad dressing, Italian, regular	0.00±0.00
Ham, cured (not canned), baked	0.59±0.11	Sour cream	0.00±0.00
Milk shake, chocolate, fast-food	0.59±0.35	Sugar, white, granulated	0.00±0.00
Mixed vegetables, frozen, boiled	0.58±0.12	Syrup, pancake	0.00±0.00

Table 5-22. Copper Content of Selected Foods (mg/kg)

Food description	Mean±SD	Food description	Mean±SD
Chicken with vegetables in sauce, from Chinese carry-out	0.57±0.13	Tea, decaffeinated, from tea bag	0.00±0.00
Muffin, blueberry	0.56±0.12	Tilapia, baked	0.00±0.00
Luncheon meat, ham	0.55±0.07	Vegetable oil	0.00±0.00
Macaroni and cheese, prepared from box mix	0.55±0.15	Yogurt, frozen, vanilla	0.00±0.00
Pear, canned in light syrup	0.55±0.22	Yogurt, low-fat, fruit-flavored	0.00±0.00

SD = standard deviation

Source: FDA 2017

Table 5-23. Copper Content of Selected Baby Foods (mg/kg)

Food description	Mean	SD
Teething biscuits	1.60	0.53
Sweet potatoes	1.24	0.22
Arrowroot cookies	1.08	0.08
Cereal, mixed, dry, prepared with water	1.01	0.18
Cereal, oatmeal with fruit, prepared with water	0.96	0.10
Pears	0.95	0.08
Peaches	0.92	0.14
Turkey and rice	0.92	0.22
Cereal, oatmeal, dry, prepared with water	0.91	0.21
Mixed vegetables	0.90	0.10
Peas	0.89	0.07
Infant formula, soy-based, ready-to-feed	0.86	0.06
Bananas	0.84	0.22
Macaroni and cheese with vegetables	0.70	0.27
Chicken noodle dinner	0.67	0.09
Pears and pineapple	0.67	0.08
Plums/prunes with apples or pears	0.65	0.18
Apricots with mixed fruit	0.64	0.20
Carrots	0.64	0.17
Macaroni, tomato, and beef	0.64	0.08
Chicken with rice	0.61	0.06
Vegetables and turkey	0.61	0.16
Apples with fruit other than berries	0.57	0.14
Green beans	0.57	0.05
Infant formula, milk-based, iron fortified, ready-to-feed	0.56	0.07
Vegetables and beef	0.56	0.10

Table 5-23. Copper Content of Selected Baby Foods (mg/kg)

Food description	Mean	SD
Squash	0.55	0.09
Fruit yogurt dessert	0.53	0.23
Vegetables and chicken	0.51	0.14
Cereal, rice, dry, prepared with water	0.46	0.04
Beef and broth/gravy	0.39	0.10
Applesauce	0.36	0.06
Juice, pear	0.34	0.04
Chicken and broth/gravy	0.33	0.02
Apples with berries	0.26	0.23
Turkey and broth/gravy	0.15	0.26
Juice, apple	0.11	0.03
Juice, grape	0.02	0.04

SD = standard deviation

Source: FDA 2017.

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.

Wu et al. (2018) conducted a review of the literature to determine nutrient composition in human milk in the United States and Canada from 1980 to 2017. Average copper levels were 0.02–0.08 µg per 100 g of human milk in women 1–6 months postpartum and 0.017–0.02 µg per 100 g of human milk in women 7–12 months postpartum.

Concentrations of copper in biota sampled across the United State are reported in Table 5-24 (WQP 2022). High concentrations of copper have been measured in shellfish and crustacean species such as shrimp and prawns, which use a copper-containing protein, hemocyanin, as an oxygen-transport molecule (Olmedo et al. 2013; Venugopal and Gopakumar 2017). Median copper concentrations ranged from 0 mg/kg wet weight in canned frigate to 6.865 mg/kg wet weight in frozen prawn (Olmedo et al. 2013). The calculated intake of copper from fish and shellfish is 0.117 mg/day, which is not expected to pose a risk to the average consumer (Olmedo et al. 2013). Shellfish provide between 7 and 378% of percent daily values of copper, with the highest contributions from oysters, squid, and lobster (Venugopal and Gopakumar 2017). 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). EPA (1980b)reported similar results for mussels (3.9–8.5 ppm) and for clams (8.4–171 ppm). Measurements of copper concentrations in zebra and quagga mussels taken from Lakes Erie and Ontario in 1997 were 21–41 ppm (dry weight) (Rutzke et al. 2000). In the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Project, copper concentrations were quantified in mollusks (*Mytilus edulis*, *Mytilus californianus*, *Crassostrea virginica*, and *Ostrea equestris*) 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.

Table 5-24. Summary of Concentrations of Copper (µg/kg) Measured in Biota Samples Across the United States

Year range/ organism	Average	Maximum concentration	Number of samples	Percent detected
2020–2022[a]	4,404	126,000	338	100%
Mylocheilus caurinus	194	4,980	48	14%
Catostomus macrocheilus	7,023	35,900	40	12%
Micropterus salmoides	198	342	39	12%
Ptychocheilus oregonensis	2,108	4,140	30	9%
Ictalurus punctatus	256	410	28	8%
Oncorhynchus mykiss	4,493	22,100	21	6%
Micropterus dolomieu	354	943	19	6%
2015–2019[b]	5,651	1,219,000	3,567	88%
M. salmoides	4,402	1,070,000	507	14%
I. punctatus	836	26,900	217	6%
M. dolomieu	967	84,830	163	5%
2010–2014[c]	4,642	394,000	2,871	91%
M. salmoides	2,932	76,000	495	17%
I. punctatus	1,212	27,000	208	7%
Mytilus edulis	4,920	58,600	194	7%
M. dolomieu	516	4,800	173	6%

[a]As of October 24, 2022; all organism (n=33) data regardless of detection frequency.
[b]All organism (n=179) data regardless of detection frequency.
[c]All organism (n=116) data regardless of detection frequency.

Source: WQP 2022

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 redear sunfish and bluegill sunfish collected from stormwater 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, 0.879 and 1.07 mg/kg wet weight, respectively, measured in controls collected in natural lakes or ponds. However, in largemouth bass, the mean copper concentrations in fish collected from stormwater ponds and controls did not significantly differ, with values of 3.81 and 4.71 mg/kg wet weight, respectively.

The copper concentrations in the liver of lake trout and grayling taken from four freshwater lakes in Alaska 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 significantly higher burdens ($p<0.05$) of copper in their livers than grayling, and the concentrations of copper in the livers of trout varied considerably depending on the lake from which they were collected. The species and site differences in copper concentrations in fish livers have been attributed to differences in diet (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.

Concentration ratios of copper in plants relative to soil (concentration factors) demonstrate that copper uptake differs significantly between plants. For example, concentration factor 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 grown in Japan were found to vary among soil types (0.59–3.58), with copper concentrations in rice of 1.7–5.1 µg/g (Herawati et al. 2000). Copper concentrations in rice grain from the Yangtze delta in China have been found to increase significantly from 1.4 to 15.5 µg/g when copper concentrations in wastewater irrigated soils increased from 17.0 mg/kg (wet weight) to 101.2 mg/kg (wet weight) (Cao and Hu 2000).

Studies of copper in human tissues suggest that copper content in a 70-kg adult ranges from 50 to 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 environment, the copper concentration in the liver only varied by a factor of 2–3.5. The concentration of copper in blood is not expected to be predictive of the total body burden of copper. Saltzman et al. (1990) found that the correlation between copper concentrations measured in blood and total body burden was poor ($r=0.54$).

Copper content in 25 tea samples from China ranged from 7.73 to 63.71 mg/kg (Zhong et al. 2015). In a study of copper release from the inner surface of copper teapots, Ni and Li (2008) found that cuprite was a main mineral component of the corrosion byproducts.

The range of copper concentrations in the filler tobacco of 10 cigarette brands manufactured by British American Tobacco and International Tobacco Company were 18.26–34.94 µg/cigarette (Benson et al. 2017). The range in the filters after smoking was 1.77–36.48 µg/g. The mean copper content of tobacco in Finnish cigarettes was 24.7±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. Copper levels of 15.4–447 ng/10 puffs were reported for four nicotine-based e-cigarette or vaping product (EVP) aerosols and 16.08 ng/10 puffs in one cannabinoid-based EVP aerosol (Gonzalez-Jimenez et al. 2021).

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 was 126–7,729 ppm (dry weight), with a median value of 991 ppm. Gutenmann et al. (1994) reported 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). The concentration of copper in cow's manure was ~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 of 22.7–327 ppm in composts formed from yard waste, 432–1,019 ppm from sewage sludge, and 191–1,143 ppm from municipal solid waste.

Bolan et al. (2003) analyzed copper in farm effluent and sludge samples at dairy and pig farms that utilized copper hydroxide and at farms that did not use copper hydroxide. The concentration of total copper was higher at farms that used the compound. Copper concentrations were higher in the sludge samples than the effluent. At dairy farms utilizing copper hydroxide, the copper concentrations were 52–

105 mg/kg in sludge and 2.5–10.5 mg/L in effluent. At pig farms utilizing copper hydroxide, copper concentrations were 12.5–526 mg/kg in sludge and 0.1–1.55 mg/L in effluent.

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 Landsberger (1995) reported concentrations of copper of 390–530 µg/g in fly ash, 1,560–2,110 µg/g in bottom ash, and 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 stack particulate matter (Balogh 1996). In fossil fuel wastes, copper concentrations were 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 (Eary et al. 1990).

Copper concentrations have been measured in several types of electronic and e-waste. The concentrations of copper were 276,186–423,727 mg/kg in discarded basic phones and 268,945–434,628 mg/kg in discarded smartphones (Singh et al. 2019). The average concentrations in basic phones and smartphones were 378,406 and 357,560 mg/kg, respectively. The average weights of copper in different electronic devices were 700,300 mg in plasma televisions, 625,600 mg in color cathode-ray tube (CRT) televisions, 206,000 mg in liquid-crystal-display (LCD) televisions, 102,800 mg in laptop computers, 59,500 mg in LCD monitors, and 18,800 mg in cell phones (Woo et al. 2016). In an assessment of hazardous chemicals in a market-representative set of waste printed circuit boards (WPCBs) originating from computers manufactured from 1996 to 2010, copper was found ranging from 177,000 to 268,000 mg/kg and was the most abundant metal in the WPCBs (Chen et al. 2016). In WPCBs, copper is used to transmit electric signals and is fundamental, but results from the study showed that technological innovation modeled by three types of Intel chipsets correlates with an overall decrease in copper concentration (Chen et al. 2016).

Copper may also be found in clothing. Herrero et al. (2020) analyzed 39 swimsuits made in Vietnam, China, Cambodia, Albania, Sri Lanka, Bangladesh, Tunisia, Spain, Morocco, and Myanmar. Copper was detected in 64% of the samples at concentrations of <0.15–328 mg/kg, with an average concentration of 27.9 mg/kg. Although Herrero et al. (2020) did not specifically discuss the origins of copper in swimsuits, the study authors do note that many swimsuits were made of artificial fibers so that they may be water repellant or fast drying. Metals may be used in the textile industry as dyes, antimicrobials, and water repellants (Herrero et al. 2020).

An assessment of trace metals in lip balms, lip glosses, and lipsticks found that copper was one of the three major trace metals found in lip cosmetics (Gao et al. 2018). Copper concentrations were 11.07–136.73 mg/kg in the products sampled; the mean concentrations were 61.96 (lip balms), 81.28 (lip glosses), and 93.93 mg/kg (lipsticks).

Copper has been detected in pigments in American tattoo ink (Liszewski and Warshaw 2019). Of 44 distinct pigments identified, 4 contained copper. All four pigments were phthalocyanine. The most frequently used pigment containing copper is found in 13 tattoo ink brands and in 562 inks; the least frequently used is found in 1 brand and 1 ink.

Concentrations of copper in fertilizers, soil amendments, and other agricultural materials have been measured by Raven and Loeppert (1997). The materials and mean concentrations are 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). Copper was measured in cement dust from the United States at an average concentration of 23.66±7.23 µg/g (Ogunbileje et al. 2013).

5.6 GENERAL POPULATION EXPOSURE

Due to the ubiquity 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 different source categories (e.g., smelters, ore processing, steel production, and combustion) yielded a maximum annual concentration of 30 µg/m^3 (EPA 1987). If a person is assumed to inhale 20 m^3 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^3 (EPA 1987), the average daily intake by inhalation, would be 0.1–4.0 µg. At the maximum reported ambient air concentration, 100 µg/m^3 for a 24-hour period at a location within one-half mile of a major source (EPA 1987), 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, <10 µm in diameter.

For adult men and women in the United States, the median intake of copper from food sources has been approximated as 1.0–1.6 mg/day (IOM 2001). Based on NHANES data in the 2020 pre-pandemic survey titled *What We Eat in America*, for all individuals aged ≥2 years, the average daily dietary intake of

copper from food is 1.1 mg/day (USDA 2020). According to the NHANES survey of all individuals aged ≥20 years, 18% reported using supplements containing copper. For individuals consuming supplements, the average daily intake from food plus supplement was 2.4 mg/day (USDA 2020). The mean nutrient intake of copper for all males aged ≥20 years from foods was 1.3 mg, and intake from foods plus supplements was 1.5 mg. The mean nutrient intake of copper from foods for all females aged ≥20 years was 1.1 mg, and intake from foods plus supplements was 1.3 mg. For those participants who were supplement users, the mean nutrient intakes of copper for males aged ≥20 years were 1.5 mg from foods and 2.6 mg from foods plus supplements and the mean nutrient intakes of copper for female supplement users aged ≥20 years were 1.1 mg from foods and 2.3 mg from foods plus supplements (USDA 2020). The dietary intake of copper is expected to be above this average for those individuals who regularly consume organ meats (e.g., liver and kidney), nuts, seeds (including cocoa powder), legumes, and bran and germ portions of grains; these intakes are not expected to exceed the maximum recommended limits of 10–12 mg/day (WHO 1996). Mammalian liver, nuts, oilseeds, cocoa powder, and chia seeds contained the highest copper concentrations in a German total diet study (Kolbaum et al. 2023). Copper concentrations appeared to be greater in organically produced foods compared to conventionally produced food, and copper intake was about 10% higher in consumers selecting organic foods. The dietary exposure for children was between 0.04 and 0.07 mg/kg body weight per day, and for adults, exposure ranged between 0.02 and 0.04 mg/kg body weight per day (Kolbaum et al. 2023). In the United States, Tolerable Upper Intake Levels (ULs) vary by life stage, ranging from 1 mg/day for 1-year-old children and 10 mg/day for adults and pregnant and lactating females ≥19 years old (Table 5-17). Those individuals who regularly consume oysters or clams may increase their dietary intake of copper by 2–150 mg/day when consuming 250 g of edible tissue per day, based on copper concentrations of 25–600 and 8.4–171 ppm in oysters and clams, respectively (EPA 1980b; Goldberg 1986).

Assuming a median copper concentration in drinking water of 75 µg/L, the average daily copper exposure from consumption of 2 L water/day would be 0.15 mg. However, people may have high levels of copper in their tap water due to transport through the water distribution system. While corrosion can occur in plumbing of any age, new copper plumbing is a potential source of exposure as copper leaches into drinking water. In the presence of certain water qualities, copper levels in excess of the EPA action level (1.3 mg/L) are most likely to occur in newly constructed homes and buildings with copper plumbing, or at sites that have been recently renovated with new copper plumbing (Edwards et al. 2001; EPA 1995; Grace et al. 2012; Knobeloch et al. 1998; Lagos et al. 2001; Rajaratnam et al. 2002; Schock and Sandvig 2009; Turek et al. 2011). If the system is not permitted to flush out, average intakes from water may be >2 mg/day. Exposure to copper via drinking water has declined significantly since the implementation of

1991 EPA Lead and Copper Rule; exceedances of the action level in the nation's water systems has decreased by over 90% (EPA 2019, 2020b). It is less likely that high dermal exposures will result from bathing in contaminated tap water because the distribution system will flush itself out as the water is drawn.

Exposure to copper compounds may occur through inhalation of aerosols from electronic cigarettes. The potential for exposure depends on the design and materials used in the construction of the aerosol devices, the liquid contents, and the number of puffs that an individual takes per day (generally between 10 and several hundred puffs per day). Copper content in aerosols from first-, second-, and fourth-generation devices ranged from <0.2 to 614 ng per 10 puffs (Halstead et al. 2020). In aerosols from fourth-generation, pod-type devices, copper levels ranged from <0.2 to 209 ng per 10 puffs (Gray et al. 2022); the range was <1.00–104 ng per 10 puffs in aerosols from first- and fourth-generation devices, depending on the specific nicotine salt used in the respective liquids (Pappas et al. 2024).

Data on serum copper for the U.S population from NHANES survey years 2013 to 2016 are presented in Table 5-25. In a 2019 cross-sectional study in China of 3,285 participants with an average age of 72.7 years, a median whole-blood copper concentration of 751.68 µg/L was reported (Guo et al. 2022b).

Table 5-25. Geometric Mean and Selected Percentiles of Serum Copper (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2016, 2018)

	Survey years	Geometric mean (95% CI)	Selected percentiles				Sample size
			50th	75th	90th	95th	
Total	13–14	1,148.34 (1,122.60–1,174.68)	1,135	1,319	1,547	1,710	2,520
	15–16	1,146.60 (1,124.94–1,168.68)	1,130	1,314	1,538	1,692	2,436
Age group							
12–19 years	13–14	1,055.83 (1,033.20–1,078.96)	1,036	1,197	1,414	1,641	418
	15–16	1,055.03 (1,012.29–1,099.57)	1,031	1,232	1,408	1,534	371
20–59 years	13–14	1,161.59 (1,129.35–1,194.75)	1,138	1,343	1,607	1,787	1,221
	15–16	1,152.32 (1,129.72–1,175.38)	1,124	1,315	1,600	1,794	1,165
≥60 years	13–14	1,149.31 (1,117.16–1,182.39)	1,165	1,310	1,472	1,599	542
	15–16	1,161.35 (1,123.66–1,200.31)	1,150	1,327	1,479	1,617	579
Sex							
Male	13–14	1,032.39 (1,001.14–1,064.63)	1,032	1,173	1,308	1,414	1,235
	15–16	1,042.57 (1,021.11–1,064.49)	1,043	1,171	1,332	1,422	1,201
Female	13–14	1,271.39 (1,246.35–1,296.93)	1,244	1,453	1,677	1,908	1,285
	15–16	1,254.96 (1,221.69–1,289.15)	1,241	1,429	1,672	1,903	1,235

Table 5-25. Geometric Mean and Selected Percentiles of Serum Copper (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2016, 2018)

	Survey years	Geometric mean (95% CI)	Selected percentiles 50th	75th	90th	95th	Sample size
Race/ethnicity							
Mexican American	13–14	1,163.47 (1,132.65–1,195.12)	1,157	1,353	1,567	1,738	431
	15–16	1,147.80 (1,118.65–1,177.70)	1,131	1,294	1,534	1,747	464
Other Hispanic	13–14	1,181.15 (1,126.79–1,238.13)	1,156	1,375	1,587	1,656	235
	15–16	1,142.06 (1,115.41–1,169.35)	1,133	1,323	1,493	1,741	334
Non-Hispanic white	13–14	1,131.74 (1,104.19–1,15997)	1,111	1,300	1,504	1,679	975
	15–16	1,134.14 (1,107.51–1,161.40)	1,117	1,295	1,476	1,652	764
Non-Hispanic black	13–14	1,250.99 (1,217.36–1,285.56)	1,242	1,469	1,653	1,763	516
	15–16	1,270.74 (1,228.30–1,314.63)	1,245	1,452	1,705	1,959	494
Other race	13–14	1,105.52 (1,075.40–1,136–49)	1,082	1,292	1,455	1,659	363
	15–16	1,091.44 (1,053.23–1,131.04)	1,095	1,231	1,486	1,653	380

CI = confidence interval

A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that potentially 920,449 workers, including 72,821 women, were occupationally exposed to copper in the United States (NIOSH 1989). The NOES estimate is provisional because all of the data for tradename products that may contain copper have not been analyzed. An estimated 11,889 workers, including 421 women were potential exposed to pure copper and an estimated 53,282 workers, including 8,758 women were potential exposed to copper powder. Additionally, according to the NOES, 16,759 workers, including 9,684 women, were potentially exposed to copper chloride and 17,248 workers, including 4,024 women, were potentially exposed to copper oxide (NIOSH 1988). The NOES was based on field surveys of 4,490 facilities and was designed as a nationwide survey based on a statistically valid 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 Safety and Health Administration (OSHA) occupational exposure limits for copper fume are 0.1 and 1 mg/m3 for dust and mists (OSHA 2023).

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 kg 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 breastmilk 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).

In a cross-sectional study, including 3,982 children and adolescents participating in NHANES survey years 1999–2006, the reported median copper dietary intake estimated for individuals aged 6–18 years was 0.98 (0.71–1.32) mg/day (Shi et al. 2023).

Children could be exposed to copper through contact with wood treated with alkaline copper quaternary (ACQ) (Cushing et al. 2007). ACQ, which contains copper oxide, is used to treat residential decks and playsets. Children might ingest ACQ from dislodged wood residues via hand to mouth contact or be exposed via dermal contact.

Exposure of copper through oral routes may differ between children and adults, 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 requirements from breastmilk is likely to be different from infants whose nutritional needs are either supplemented or entirely received through the consumption of formula. Estimates of copper intake from inhalation and ingestion in children in the United States are limited. From the work of Pennington et al. (1986), the copper intakes from food consumption for a 6–11-month-old infant and a 2-year-old child were estimated to be 0.47 and 0.58 mg/day, respectively, values that are lower than the adult intake of ~1 mg/day. One study provided estimated inhalation and ingestion exposures of copper for 6–10-year-old children in India (Raghunath et al. 1997). In this work, mean daily concentrations of copper in particulates in air from six locations were measured at 0.01–0.26 µg/m^3. Based on these measurements, estimated inhalation exposures of children to copper were calculated to be 0.1–3.2 µg/day; exposures to copper through ingestion were estimated to be 684–1,732 µg/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 in a polluted area near a lead smelter in Yugoslavia, as measured by copper concentration in teeth, increased in children living closer to the smelter (Blanuša et al. 1990). A study conducted in an industrial area of Northwest China in which concentrations of copper were measured in street dust samples collected from a commercial area, residential area, scientific and educational area, and

an industrial and mining area demonstrated higher concentrations of copper in the industrial and mining area posed a noncarcinogenic risk to preschool children in the area (Zhang et al. 2023b). 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). Copper-contaminated drinking water has been reported to create a light blue or blue-green color to water, and may result in a metallic, bitter taste (WHO 2004). 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.

Arcega-Cabrera and Fargher (2016) measured copper in blood and urine samples of children in Mexico and found that 79.4% had copper detected in urine and 100% had copper detected in blood. The ranges of median copper were 723.02–1,143.7 µg/dL in blood at nine elementary schools and from below detection limit to 20.62 µg/dL in urine. Using ethnographic data, Arcega-Cabrera and Fargher (2016) identified potential sources and pathways of exposure to metals. They concluded that children from poor or marginalized families tended to be exposed to copper while children from wealthier families tended to be exposed to inorganic copper (copper sulfate). There was a positive correlation between the frequency that children ate fresh fish and copper in blood, while there was a negative correlation between the frequency and copper in urine. This is likely due to the copper in fish being protein-bound. Since copper sulfate is used as a preservative in fresh fish and as a water treatment in ponds and other freshwater surfaces, children who eat fresh fish more often may be exposed to it. Piped or well water in the study was found to contain higher levels of copper than purified water, and children of poorer or more marginalized families who cooked with piped or well water had higher levels of copper in urine. Children from households cooking over open food fires also had higher levels of copper in urine than households cooking with gas.

5.7 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) ions and perhaps some weakly complexed or adsorbed small particulate copper ions. The data indicate that copper in natural water, sediment, and soil mainly exists in bound form. Even so, the free form of copper may be released from ingested materials due to the acidic pH encountered in the stomach. Potential for high uptakes of copper in the general population may exist in situations where people consume large amounts of tap water that contains dissolved copper that come from corrosion of copper in the distribution system, or already have 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 system materials is likely to occur where the water is soft and not flushed out of the system by running the water down the drain before collecting some of it for use. In such cases, the initial concentration of copper frequently exceeds 1 ppm. A large fraction of the copper may be in the form of free cupric ion, and uptake will result by ingestion and, perhaps, dermal contact. Soluble cupric salts are used extensively in agriculture and in water treatment. Workers engaged in the formulation and application of these chemicals along with industrial workers, such as those in the plating industry, may come into dermal contact with absorbable copper ions. Exposure to high levels of free Cu(II) can occur, for example, from swimming in water that was recently treated with a copper-containing algaecide.

Exposure to environmental tobacco smoke may contribute to increased copper exposure in children. Gatzke-Kopp et al. (2023) identified a positive correlation of salivary levels of copper in children and exposure to environmental tobacco smoke.

In a study in Nigeria, serum concentrations of copper were significantly elevated in users of skin-whitening agents (Iyanda et al. 2011). Copper concentrations were 2.27–8.48 mg/kg in toning and skin lightening creams sold in Nigeria (Sani et al. 2016; Theresa et al. 2011), and higher concentrations (8.8–17.85 mg/kg) were detected in moisturizing creams (Theresa et al. 2011). Thus, in some countries, consumers who use moisturizers, toning creams, or skin-whitening agents could be at risk of higher exposure to copper.

Based on the available data, people living close to NPL sites may be at greater risk for exposure to copper than the general population. In this case, exposure can occur through inhalation of airborne particulates from the NPL sites, ingestion of water from private wells near the sites, ingestion of contaminated soil, and/or uptake of copper into fruits and vegetables raised in gardens of residents living near NPL sites.

People living near copper smelters and refineries, as well as workers within these and other industries, can be exposed to high levels of dust-borne copper by both inhalation and ingestion. In some industries, workers may be exposed to fumes or very fine dust that may be more hazardous than coarse-grained dust, because it can be inhaled and penetrate more deeply into the lung, thereby evading the mucociliary escalator.

A health surveillance assessment conducted at a copper smelter, using historical monitoring data of inhalable copper dust collected between 1982 and 2018, found that smelter workers can be exposed via

inhalation to copper at exposure levels averaging 4.61±2.13 mg/m^3-years (Haase et al. 2021). Occupational exposure of foundry workers via inhalation was evaluated in 197 male employees from a Brazilian ferrous foundry plant (Freire et al. 2021). Airborne concentrations of copper ranged between below the detection limit of 0.00003 and 8.8 µg/m^3, with a mean value of 1.9±2.1 µg/m^3. Biological monitoring of the workers found concentrations of 0.6–295 µg/L (mean 13.1±21.3) and 674–1,221 µg/L (mean 962±114) in urine and blood samples, respectively. In a 2011 study, urinary metal concentrations and estimated airborne exposure were analyzed to determine occupational exposure in both men and woman employed in welding and electrical trades. Copper was found at concentrations >4.527 µg/L in 18.7% of welders and 15.0% of electricians (Galarneau et al. 2022). Mean urinary concentrations were 13.24±12.52 (log-transformed concentration 2.37±0.61) and 13.07±8.48 (log-transformed concentration 2.41±0.57) in samples from welding trades and electrical trades, respectively.

Exposure to ultrafine particles of copper poses a risk to human health due to their smaller size, larger surface area, surface material, and physical characteristics (Schraufnagel 2020). Traffic exhaust is a common source of exposure, although homes near a trash burning site, bedrooms with burning coils for mosquito abatement, homes with smokers, and kitchens during domestic cooking are also sources of exposure to ultrafine particles (Schraufnagel 2020). Particles created by brake wear, including copper particles, are in the range of 2.8 µm (Wåhlin et al. 2006). Copper has been identified in ultrafine particles leading to metal fume fever among welders (Schraufnagel 2020).

CHAPTER 6. 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 NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of copper.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

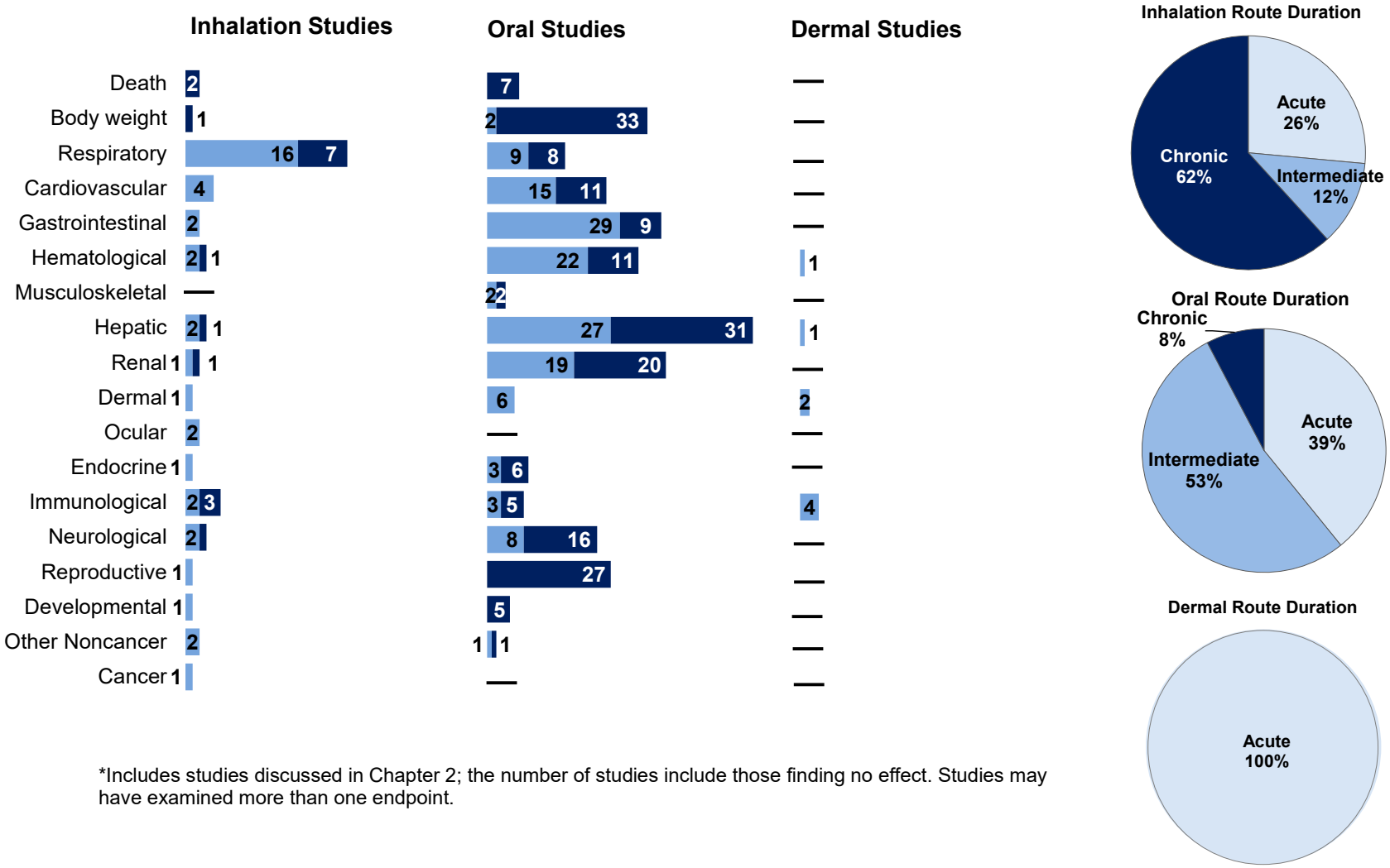
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to copper that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of copper. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As shown in Figure 6-1, information on the health effects in humans exposed to copper primarily apply to oral ingestion. Many of these studies are case reports of individuals who intentionally or accidentally ingested copper or copper-containing substances. Epidemiological and controlled-exposure studies in humans primarily examined effects following ingestion of copper in drinking water. In these studies, gastrointestinal symptoms were the most frequently observed health effect. There are a robust number of experimental studies in animals that examine a wide range of health effects following oral exposure to copper and/or copper compounds, particularly the hepatic and renal toxicity endpoints. Inhalation and dermal studies were limited in both animals and humans, but the results generally support the effects following oral ingestion.

Figure 6-1. Summary of Existing Health Effects Studies on Copper by Route and Endpoint*

Potential gastrointestinal and hepatic effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Studies may have examined more than one endpoint.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not 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* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The acute-duration oral database was adequate for the derivation of an acute-duration oral MRL. The acute-duration inhalation database was not adequate for the derivation of an acute-duration inhalation MRL. Studies examining toxicity from inhalation of copper particles would be useful to identify or confirm the target(s) of toxicity via this exposure route.

Intermediate-Duration MRLs. The intermediate-duration oral database provided support for the adoption of the acute-duration oral MRL. Additional studies are not likely to modify the intermediate-duration oral MRL. The intermediate-duration inhalation database was not adequate for the derivation of an inhalation MRL. Studies examining toxicity from inhalation of copper particles would be useful to identify or confirm the target(s) of toxicity via this exposure route.

Chronic-Duration MRLs. The chronic-duration oral database was not adequate for the derivation of a chronic-duration oral MRL. In addition, chronic-duration inhalation studies of copper in either humans or animals were not located. Studies examining toxicity from chronic-duration oral and inhalation of copper would be useful to identify target(s) of toxicity and exposure-response relationships.

Health Effects.

Respiratory. Occupational health studies reported respiratory symptoms in workers exposed to copper dusts (Askergren and Mellgren 1975; Suciu et al. 1981). In addition, epidemiological studies of respiratory effects in workers exposed by inhalation reported increased respiratory symptoms, as well as associations between copper exposure and diminished pulmonary function as measured by spirometry (Fouad and Ramadan 2022; Mourad and El-Sherif 2022; Saadiani et al. 2023). Well-designed, high quality epidemiological studies of respiratory effects in humans exposed to copper by inhalation are needed to establish exposure-response relationships in humans. Such studies must appropriately account for coexposures and confounders. A well-conducted rat study demonstrated respiratory effects after inhalation exposure to copper

compounds (Poland et al. 2022); studies in mice or other species would be beneficial. Studies of respiratory effects after oral exposure are adequate to demonstrate that the respiratory tract is affected only at high oral doses.

Immunological. Limited evidence in humans and animals suggests that excess copper may be immunotoxic. A study in adult men found that antibodies to an influenza strain were decreased after immunization when compared to controls following exposure to 0.1 mg Cu/kg/day (Turnlund et al. 2004). Immunological effects were observed in mice following acute-duration inhalation exposure to copper sulfate (Drummond et al. 1986). Copper produced a toxic effect on the antioxidant defense system in mice; decreased percentages of suppressor, natural killer, and precursor cells, along with increased immunoregulatory index were reported (Kvietkauskaite et al. 2004). More studies in humans and detailed immunotoxicity studies in animals exposed orally or by inhalation are needed to establish dose-response relationships for immune system effects.

Neurological. A well-conducted prospective cohort study in the United States reported an association between intake of dietary copper >1 mg Cu/day and incident dementia (Wei et al. 2022). Support for neurological effects of copper comes from animal studies demonstrating neurobehavioral changes (Adeleke et al. 2023; Isibor et al. 2022; Kalita et al. 2020; Kumar et al. 2015, 2016a, 2016b, 2019; Patwa et al. 2022; Yu et al. 2023), altered brain neurotransmitter levels (De Vries et al. 1986; Isibor et al. 2022; Murthy et al. 1981), and brain histopathological changes (Adeleke et al. 2023; Arowoogun et al. 2021; Kumar et al. 2015, 2016a, 2016b; NTP 1993). Furthermore, mechanistic investigations (see Section 2.21) provide a biological basis for such neurological effects. Additional epidemiological studies of oral exposure to copper and neurological diseases would be beneficial to provide an adequate database for identification of neurological hazards and dose-response relationships.

Developmental. Studies of developmental effects in animals exposed to copper by oral administration include a combined repeat-dose and reproductive/developmental toxicity screening study in rats (Chung et al. 2009) and studies in mice, mink, and rats exposed pre- or postnatally that examined limited endpoints and/or had deficiencies in reporting (Aulerich et al. 1982; Fuentealba et al. 2000; Lecyk 1980). Available studies did not conduct comprehensive evaluations for malformations and variations; thus, additional, well-conducted studies including these endpoints are needed. No studies of developmental toxicity in animals exposed by

inhalation or dermal contact were located, reflecting a gap in the available data on developmental effects.

Cancer. Available studies on the carcinogenicity of copper in humans and animals are inadequate. Additional studies by the inhalation, oral, and dermal routes are needed to assess the carcinogenic potential of copper in humans and/or animals.

Genotoxicity. The genotoxicity of copper and compounds has been extensively studied. Additional studies are not warranted unless new copper compounds enter the marketplace.

Epidemiology and Human Dosimetry Studies. The epidemiological database for copper is extensive, but a large majority of the studies used biomarkers of exposure (blood, tissue levels) that can be affected by health conditions, intake of other minerals, and other factors. More studies that quantify exogenous and dietary/supplement exposure to copper may help to further evaluate the potential relationship between excess oral copper intake and neurodegenerative diseases. In addition, epidemiological studies that evaluate the concentration-response relationship between inhalation exposure to copper compounds and respiratory effects would be beneficial.

Biomarkers of Exposure and Effect. Copper levels can be measured in tissues, body fluids, excreta, hair, and nails. Whole blood, serum, and urine copper levels have been established in healthy individuals. It has been demonstrated that copper levels in the body increase with increased exposure after acute poisoning. Similarly, increased copper levels were observed in workers after occupational exposure. Serum and urine copper levels, plasma ceruloplasmin levels, and clinical manifestations are specific indicators of copper status. Current biomarkers appear sufficient for assessing copper exposure.

There are no specific biomarkers of effect 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 is not known. Studies examining the possible correlation between blood levels or excreta levels of copper with effects would facilitate medical surveillance. Liver enzyme levels can indicate liver damage resulting from copper toxicity; however, these are not specific to copper-induced liver damage.

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 compounds and differences between the bioavailability of copper from food and water.

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 from both the inhalation route and the dermal route would more fully characterize copper toxicokinetics in animals and by extrapolation in humans.

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 might serve as the best model for extrapolating results to humans is not known. Additional studies to address comparative toxicokinetic data gaps would be beneficial.

Children's Susceptibility. There are some data on the toxicity of copper in infants and 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: ICC and ICT. Both of these syndromes have been connected to elevated copper intakes 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 ascertain copper's role in the observed effects.

Physical and Chemical Properties. In general, the available data on the physical and chemical properties of elemental copper and the copper compounds listed in Table 4-1 are sufficient for estimating the environmental fate of copper. Experimental confirmation is ideal for predicting copper's fate in the environment. The factors that determine the copper species present and/or the material to which copper may be bound and the strength of the binding is usually material- and 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, experimental confirmation is necessary.

Production, Import/Export, Use, Release, and Disposal. Information on the production, use, release, and disposal of metallic copper and copper sulfate is generally available. Copper and copper

sulfate are the two forms of copper that account for most of the copper used. This information is tabulated by the USGS every year in the Minerals Yearbook, and predictions of future trends in production and use are available. Information on the future of copper demand and implications on copper recycling and production are also available (Ciacci et al. 2020; Schipper et al. 2018). The major uses of copper and where these uses occur (e.g., the home, workplace, etc.) are also available. Such information is not available for many other copper compounds of lesser use.

Environmental Fate. Reliable 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 extensively available. Data on its transport in the environment are also reliable. 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 identify numerous contributors to the fate of copper and its compounds, but they are insufficiently comprehensive for developing accurate fate maps. In addition, studies of how fate data relate to human exposures, especially with regard 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. 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 that do not include hazardous waste sites. More information on the forms of copper found at industrial sites and hazardous waste sites would be useful. Monitoring groundwater near industries that use highly acid, copper-containing solutions, such as electroplating, electrowinning, and ore leaching industries, is important for the protection of human populations at risk of exposure to their highly mobile and highly bioavailable copper.

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

foodstuffs from apparently polluted areas or where they may have accumulated toxic levels of copper through biomagnification resulting from foraging in polluted areas.

Exposure Levels in Environmental Media. Data are 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, trace quantitative analytical and statistical techniques can be used to determine whether the copper found at these sites is elevated above background levels. Monitoring data are reasonably current and human intake of copper from food, water, and air can be estimated.

Exposure Levels in Humans. There are reasonably current data on levels of copper in human tissue and human milk. However, few studies address specific U.S. populations living around hazardous waste sites. There are some quantitative data relating occupation, level, and route of exposure to the form of copper to which people are exposed. There is some limited information correlating copper concentration and form to body burden in the general population. However, more information is needed for occupational and other at-risk populations.

Exposures of Children. Data on copper intake in infants and children is generally up to date. Information on copper intake by 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 and implemented. However, only limited information on inhalation 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 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 establishing the validity of these surrogates is underway.

6.3 ONGOING STUDIES

Table 6-1 lists research studies identified in a search of the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER 2024) that are currently being conducted that may fill some of the data needs discussed in Section 6.2.

Table 6-1. Ongoing Studies on Copper

Investigator	Affiliation	Research description	Sponsor
Dr. Alicia Lane	Emory University	Metabolic mechanisms of copper-dependent neurodegeneration and excitability in menkes disease	National Institute of Neurological Disorders and Stroke
Dr. Marc Weisskopf	Harvard School of Public Health	Child and adult metal exposures, gene expression and neuropathologically confirmed Alzheimer's disease	National Institute on Aging
Dr. Diane Berengere Re	Columbia University Health Sciences	Neurotoxic and neurodegenerative risks from chronic-duration exposure to metal mixtures in e-cigarette aerosol	National Institute of Environmental Health Sciences
Dr. Shoshannah Iylene Eggers	University of Iowa	Early life metal exposure, the gut microbiome, and neurodevelopment in childhood	National Institute of Environmental Health Sciences
Dr. Peng Yuan	Icahn School of Medicine at Mount Sinai	Molecular mechanisms of copper transport	National Institute of Neurological Disorders and Stroke
Dr. Katherine Elizabeth Vest	University of Cincinnati	Function and regulation of copper in mammalian tissue differentiation	National Institute of General Medical Sciences
Dr. Ryan Loren Peterson	Texas State University	Mechanisms for cellular copper import via secreted cuproproteins	National Institute of General Medical Sciences
Dr. Heather R Lucas	Virginia Commonwealth University	Alpha-synuclein assemblies and metal-mediated redox mechanisms	National Institute of General Medical Sciences
Dr. Ji Miao	Boston Children’s Hospital	Copper and copper-binding proteins in insulin resistance-associated metabolic disease	National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Donita C Brady	University of Pennsylvania	Molecular and cellular mechanisms of copper-dependent nutrient signaling and metabolism	National Institute of General Medical Sciences
Dr. Megan K Horton	Icahn School of Medicine at Mount Sinai	Metal mixtures, exposure windows, and neurodevelopmental trajectories from adolescence to adulthood	National Institute of Environmental Health Sciences
Dr. Teresita Del Nino Jesus Padilla-Benavides	Wesleyan University	Mechanisms of copper-binding factors to promote myogenic gene expression	National Institute of Arthritis and Musculoskeletal and Skin Diseases
Dr. Tai-Yen Chen	University of Houston	Quantitative copper-homeostasis in live mammalian cells at the single-molecule level	National Institute of General Medical Sciences
Dr. Jason L Burkhead	University of Alaska Anchorage	The Atp7b-/- mouse model of neurological copper toxicity and Wilson Disease	National Institute of Neurological Disorders and Stroke

Source: RePORTER (2024)

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding copper in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for copper.

Table 7-1. Regulations and Guidelines Applicable to Copper and Copper Sulfate

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 1988
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	No health advisories listed	EPA 2018b
	National primary drinking water regulations Copper TT action level[a]	 1.3 mg/L	EPA 2022d
	National secondary drinking water regulations[b] Copper secondary MCL	 1.0 mg/L	EPA 2009a
	RfD	Not evaluated	IRIS 1988
WHO	Drinking water quality guidelines Copper guideline value	 2 mg/L (2,000 µg/L)	WHO 2022
FDA	Allowable level of copper in bottled water	1.0 mg/L	FDA 2022
	Direct food substances affirmed as generally recognized as safe when used as a nutrient supplement or as a processing aid Copper sulfate Copper gluconate	 GRAS GRAS	FDA 2019a, FDA 2019b
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification Copper	 D[c]	IRIS 1988
IARC	Carcinogenicity classification Copper 8-hydroxyquinoline	 Group 3[d]	IARC 1987

Table 7-1. Regulations and Guidelines Applicable to Copper and Copper Sulfate

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA for general industry, construction and shipyards)		OSHA 2020a, 2020b, 2020c
	Copper dusts and mists	1 mg/m^3	
	Copper fume	0.1 mg/m^3	
NIOSH	REL (up to 10-hour TWA)		NIOSH 2019a, 2019b
	Copper (dust and mists, as Cu)	1 mg/m^3	
	Copper fume (as Cu)	0.1 mg/m^3	
	IDLH		
	Copper (dust and mists, as Cu)	100 mg Cu/m^3	
	Emergency Criteria		
EPA	AEGLs	No data	EPA 2018c
DOE	PACs-air		DOE 2018
	Copper		
	PAC-1[e]	3 mg/m^3	
	PAC-2[e]	33 mg/m^3	
	PAC-3[e]	200 mg/m^3	
	Copper sulfate		
	PAC-1[e]	7.5 mg/m^3	
	PAC-2[e]	9.9 mg/m^3	
	PAC-3[e]	59 mg/m^3	
	Copper (II) chloride		
	PAC-1[e]	6.3 mg/m^3	
	PAC-2[e]	69 mg/m^3	
	PAC-3[e]	420 mg/m^3	

[a]A treatment technique (TT) is a required process, triggered by exceedance of the action level, which is intended to reduce the level of a contaminant in drinking water. The copper action level is exceeded if the 90th percentile concentration of copper is >1.3 mg/L.
[b]National secondary drinking water regulations are contaminants tested on voluntary basis. The levels indicated may cause water to appear cloudy or colored, or to taste or smell, however, it is safe to drink.
[c]D: not classified.
[d]Group 3: Not classifiable as to its carcinogenicity to humans.
[e]Definitions of PAC terminology are available from DOE (2023).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life of Health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TT = treatment technique; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL as available studies are limited and suggested serious effects at the lowest exposure levels.

Rationale for Not Deriving an MRL: Available studies of human inhalation exposure to copper and compounds were not sufficient to identify effect levels. Human studies on acute-duration inhalation exposure that met inclusion criteria include one experimental study of five men exposed to copper-only welding fume (Markert et al. 2016), occupational studies reporting metal fume fever in workers exposed to copper dust or fumes (Armstrong et al. 1983; Gleason 1968), and human case reports of accidental inhalation exposure (Donoso et al. 2007; Gibson et al. 2011). The only endpoint evaluated in the controlled exposure study (Markert et al. 2016) was serum C-reactive protein, which is an inadequate basis for determining a LOAEL or NOAEL. Neither the occupational studies nor case reports provided adequate exposure concentration information, precluding their use for MRL derivation.

Two acute-duration inhalation studies in animals exposed to copper compounds were located (Drummond et al. 1986; Poland et al. 2022). Poland et al. (2022) conducted 2-week studies of rats exposed to copper sulfate pentahydrate or dicopper oxide. In that study, LOAELs of 0.71 and 1.78 mg Cu/m^3, respectively, were identified for respiratory effects (alveolar histiocytosis, bronchioloalveolar hyperplasia, and/or increased lung weight) (Poland et al. 2022). NOAELs in this study were 0.18 and 0.71 mg Cu/m^3, respectively.

The second study (Drummond et al. 1986) involved acute-duration inhalation exposure to copper sulfate, and included evaluations of lethality, respiratory, and immunological effects in mice and limited respiratory effects in hamsters. However, the exposure concentrations reported in the study are uncertain; therefore, effect levels could not be determined. Drummond et al. (1986) reported exposure concentrations both in terms of sulfate (reporting values of 0.09, 0.1, 0.43, 0.93, and 2.53 mg SO_4/m^3) and in terms of "calculated mg metal/m^3" (reporting values of 0.12, 0.13, 0.56, 1.21, and 3.3 mg metal/m^3, respectively). The reported copper concentrations are inconsistent with the concentrations reported in terms of sulfate. For example, the copper concentration (from copper sulfate) corresponding to 2.53 mg SO_4/m^3 would be 1.67 mg Cu/m^3 (calculated as mg SO_4/m^3 x [molecular weight of copper/molecular weight of sulfate]). Copper concentrations based on the reported sulfate concentrations would be 0.06, 0.07, 0.28, 0.62, and 1.67 mg Cu/m^3, respectively. This discrepancy was limited to the copper concentrations, as the aluminum concentrations reported as "mg metal/m^3" for exposures to aluminum sulfate compounds in the study were consistent with the corresponding sulfate concentrations. It is uncertain whether the study authors incorrectly reported the sulfate concentrations or the copper concentrations for the copper sulfate exposures.

In the mouse studies (Drummond et al. 1986), increased mortality was seen at the lowest exposures, at reported sulfate concentrations of 0.09–0.1 mg SO_4/m^3. Copper concentrations corresponding to these sulfate concentrations would be 0.06–0.07 mg Cu/m^3, much lower than the NOAELs identified in the 2-week rat studies (Poland et al. 2022). Alternatively, if the "calculated mg metal/m^3" concentrations are correct, mortalities would be at concentrations of 0.12–0.13 mg Cu/m^3; these concentrations are slightly lower than the NOAEL of 0.18 mg Cu/m^3 for rats exposed to copper sulfate pentahydrate in the study by

Poland et al. (2022). No other studies of mice exposed to copper compounds by inhalation were located. In addition, no rat studies examining immunotoxicity endpoints such as those evaluated by Drummond et al. (1986) were located. In the absence of studies that refute the mortality findings at low exposure concentrations reported by Drummond et al. (1986), the available data are not considered adequate for MRL derivation, because NOAELs in the rat studies were at exposure concentrations higher than those inducing mortality in mice.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL as available studies evaluated limited endpoints and were not sufficient to establish the critical effect of intermediate-duration inhalation exposure.

Rationale for Not Deriving an MRL: One human study of intermediate-duration inhalation exposure met inclusion criteria: a case-control study of general population exposure to copper in particulate matter (Rammah et al. 2019). In this study, no association was observed between risk of stillbirth and modeled copper concentration in $PM_{2.5}$ during pregnancy (Rammah et al. 2019). These data do not provide an adequate basis for MRL derivation. Animal toxicity studies include two studies in rabbits that only identified NOAELs for respiratory and immune effects (Johansson et al. 1983, 1984) and a comprehensive study of rats exposed to dicopper oxide by inhalation for 4 weeks that identified a NOAEL and LOAEL of 0.18 and 0.35 mg Cu/m^3, respectively, for respiratory effects including alveolar histiocytosis, bronchioloalveolar hyperplasia, and/or increased lung weights (Poland et al. 2022). The available studies examined a limited number of potential endpoints, and there is uncertainty regarding whether the respiratory tract is the most sensitive target tissue. Therefore, an intermediate-duration inhalation MRL could not be derived.

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL as available data do not clearly identify a critical effect.

Rationale for Not Deriving an MRL: Human studies of chronic-duration inhalation exposure to copper that met inclusion criteria include occupational exposure studies (Askergren and Mellgren 1975; Finelli et al. 1981; Fouad and Ramadan 2022; Mourad and El-Sherif 2022; Saadiani et al. 2013; Suciu et al. 1981) and cohort studies of general population exposure to copper in airborne particular matter (Boogaard et al. 2013; Gehring et al. 2015; Ostro et al. 2015; Peralta et al. 2021; Yu et al. 2021b). The occupational exposure studies are limited because the workers were simultaneously exposed to several other heavy metals, and it was not possible to discern effects of copper alone.

Boogaard et al. (2013) evaluated the change in spirometry parameters before and after implementation of traffic reduction measures in the Netherlands, and observed improvement in FVC with a decrease of 27.2 ng Cu/m^3 in mean copper concentration in ambient air. Two cohort studies examined the association between modeled concentrations of copper in ambient particulate matter and cardiovascular outcomes (Ostro et al. 2015; Peralta et al. 2021). In a cohort of 101,884 current and former female teachers and administrators, Ostro et al. (2015) observed an association between increased mortality from ischemic heart disease and increased copper concentration in particulate matter. In a cohort study of 563 older men in Massachusetts (Peralta et al. 2021), copper concentrations in $PM_{2.5}$ were associated with decreased (improved) heart-rate-corrected QT interval. These data are insufficient to identify a critical effect of chronic-duration inhalation exposure to copper.

No chronic-duration inhalation animal studies were located.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.02 mg/kg/day
Critical Effect: Gastrointestinal effects
Reference: Pizarro et al. 1999
Point of Departure: $BMDL_{10}$ of 0.055 mg/kg/day
Uncertainty Factor: 3
LSE Graph Key: 6
Species: Human

MRL Summary: An acute-duration oral MRL of 0.02 mg Cu/kg/day was derived for copper based on gastrointestinal effects of abdominal pain, vomiting, and nausea in female adults ingesting copper sulfate in drinking water for 2 weeks (Pizarro et al. 1999). The MRL is based on a benchmark dose lower confidence limit associated with 10% extra risk ($BMDL_{10}$) of 0.055 mg/kg/day, which was divided by a total uncertainty factor of 3 for human variability; a partial uncertainty factor was applied because the direct effects of copper on the gastrointestinal tract are unlikely to be substantially impacted by toxicokinetic differences among individuals.

The acute-duration oral MRL of 0.02 mg Cu/kg/day reflects the intake of administered copper in addition to dietary background. It is intended to protect against gastrointestinal effects in people who receive adequate copper intake from diet and/or supplements. People who have copper deficiency may be given therapeutic doses at or above the MRL.

It should be noted that the acute-duration oral MRL may or may not be adequately protective for people with Wilson's disease, as the degree of protection will depend on their dietary and water intake levels as well as the degree to which their disease is medically controlled.

Selection of the Critical Effect: Numerous experimental studies and case reports support the identification of the gastrointestinal tract as a sensitive endpoint of toxicity in humans acutely exposed to copper in drinking water or in contaminated beverages (Araya et al. 2001, 2003a, 2003c; Chuttani et al. 1965; Gotteland et al. 2001; Knobeloch et al. 1994; Olivares et al. 2001; Pizarro et al. 1999, 2001; Spitalny et al. 1984).

Controlled exposure studies provide the most reliable information on gastrointestinal effects in humans, including dose-response information. Table A-1 shows NOAEL and LOAEL values for acute-duration controlled oral exposure studies in humans. It should be noted that the NOAEL and LOAEL doses reflect supplemented copper and do not include contributions from dietary intake or tap water. As the table shows, the controlled exposure studies demonstrate LOAELs between 0.012 and 0.1 mg Cu/kg/day for nausea, vomiting, abdominal pain, and/or delayed gastric emptying.

Table A-1. Summary of Gastrointestinal NOAEL and LOAEL Values in Humans after Acute-Duration Oral Exposure to Copper

Number and sex of subjects	Exposure conditions	NOAEL in mg Cu/kg/day	LOAEL in mg Cu/kg/day	Effect	Reference
30 male and 31 female healthy adults (mean ages 28.7 and 32 years, respectively)	Once as 200 mL bolus after overnight fast	0.006 (2 mg Cu/L)	0.012 (4 mg Cu/L)	Nausea in 5/53 subjects	Olivares et al. 2001
179 adult men and women (median age ~40 years)	Once as 200 mL bolus after overnight fast	0.012 (4 mg Cu/L)	0.018 (6 mg Cu/L)	Increased frequency of nausea in 17/179 subjects	Araya et al. 2001
269 healthy adult women (median ages 27–37 years across groups)	Once as 200 mL bolus after overnight fast	0.012 (4 mg Cu/L)	0.018 (6 mg Cu/L)	Nausea in 50/269 subjects	Araya et al. 2003c
15 male and 16 female healthy adults (mean age 32 years)	Once as 200 mL bolus after overnight fast	ND	0.03 (10 mg Cu/L)	Nausea (6/31 subjects) and vomiting (2/31 subjects)	Gotteland et al. 2001
15 male and 16 female healthy adults (mean ages 37 and 33 years, respectively)	Once as 300 mL bolus after overnight fast	ND	0.046 (10 mg Cu/L)	Nausea in 9/30 subjects; delayed gastric emptying	Araya et al. 2003a
60 healthy adult women (mean age 32–36 years across groups)	2 weeks, daily in water (plain, as tea, or with powdered juice mix)	0.03 (1 mg Cu/L)	0.07 (3 mg Cu/L)	Abdominal pain, nausea, and/or vomiting	Pizarro et al. 1999
45 healthy adult women (mean age 25.6 years)	1 week daily in water (plain, as tea, or with powdered juice mix)	ND	0.1 (5 mg Cu/L)	Nausea, vomiting, and/or abdominal pain	Pizarro et al. 2001

LOAEL = lowest-observed adverse-effect level; NOAEL = no-observed-adverse-effect level; ND = not determined

Animal studies have identified gastrointestinal, hepatic, renal, and reproductive system effects at much higher doses (≥2 mg Cu/kg/day) following acute-duration oral exposure to copper. Since the dietary requirement for copper is much higher in rodents (0.5–1 mg Cu/kg/day) than in humans (0.013 mg Cu/kg/day for a 70-kg human), it is not surprising that rodents tolerate higher doses. Given that there are several well-conducted controlled experiments in humans that identify effect levels lower than any of the animal studies, and laboratory animals' dietary requirement exceeds the dietary requirement in humans by more than 30-fold, only human studies were considered for MRL derivation. The human studies consistently demonstrate gastrointestinal symptoms of nausea and vomiting as the critical effect of acute-duration oral exposure to copper.

Selection of the Principal Study: The study by Pizarro et al. (1999) was selected for derivation of the acute-duration oral MRL. While Pizarro et al. (1999) did not identify the lowest LOAEL, subjects in the studies by Araya et al. (2001, 2003a, 2003c), Gotteland et al. (2001), and Olivares et al. (2001) were exposed via bolus dosing after an overnight fast, while subjects in the study by Pizarro et al. (1999) consumed the copper-containing water over the course of the day. Bolus dosing may exacerbate gastrointestinal effects that are attributable to direct contact, as the amount of copper in contact with the stomach lining is much higher. In contrast, intermittent consumption of copper-containing water over the day more closely approximates environmental exposure conditions. Furthermore, the subjects in the study by Pizarro et al. (1999) were exposed for 2 weeks, while subjects in the studies by Araya et al. (2001, 2003a, 2003c) and Gotteland et al. (2001) were exposed on a single day. Finally, of the available controlled exposure studies, only Pizarro et al. (1999) provided information on both dietary copper intake and copper concentrations in household tap water. Thus, Pizarro et al. (1999) was selected as the principal study.

Summary of the Principal Study:

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.

A group of 60 healthy women in Chile were divided into four exposure sequence groups, with mean ages within each group of 32.9–36.3 years. The mean body weight of the participants was 64 kg. Each group consumed water containing 0, 1, 3, or 5 mg/L ionic copper as copper sulfate pentahydrate (0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day, respectively) for a 2-week period followed by a 1-week rest, followed by the next dose of copper in the sequence. Each group of women was assigned to a different order of copper concentrations to consume over an 11-week period. For example, the first group was assigned to consume the control group drinking water for 2 weeks followed by a 1-week rest period, then drank the water containing 1 mg Cu/L for 2 weeks followed by a 1-week rest. This process continued in the same group with the water containing 3 and 5 mg Cu/L. Ultimately, each dose was tested in all 60 women; therefore, there were 60 women in each dose group, and each woman served as her own control. Each week, the women received a bottle containing copper sulfate solution and were asked to mix the contents of the bottle with 3 L of their drinking water. The subjects recorded daily water consumption and reported any symptoms during each 2-week exposure period. If a participant presented diarrhea, abdominal pain, or vomiting, they were told not to ingest copper-containing water for the next 2 days and consumption began once symptoms disappeared. 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 levels of serum copper, AST, ALT, and GGT activities, and hemoglobin. The average dietary intake of copper in study participants, based on a 24-hour dietary recall, was 1.7 mg Cu/day (0.0266 mg Cu/kg/day using the study-reported average body weight of 64 kg). The study authors measured the copper content of the subjects' tap water, and found it to be <0.1 mg/L.

Daily doses of supplemental copper (not including dietary or tap water contributions) were calculated using reported daily intake of copper from the copper sulfate solution (0.04, 1.74, 4.68, and 7.94 mg) and the average of the mean reported body weights across the four groups (64 kg). Daily doses were 0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg/day for exposure concentrations of 0, 1, 3, and 5 mg Cu/L, respectively. No significant alterations in levels of serum copper, ceruloplasmin, hemoglobin, or liver enzymes were observed. Twenty-one subjects reported gastrointestinal symptoms, predominantly nausea, at some point during the study period. Nine of those subjects reported 12 episodes of diarrhea with or without abdominal pain, and the study authors reported no association between copper concentration in water and diarrhea. Eight of these episodes of diarrhea occurred during the 2 weeks of the study, independent of copper concentration. Twelve subjects reported abdominal pain, nausea, and/or vomiting;

the incidences were 3/60, 1/60, 10/60, and 9/60 in the 0, 0.0272, 0.0731, and 0.124 mg Cu/kg/day groups, respectively (see Table A-2). There was a significant difference between the incidences at concentrations of ≤1 mg Cu/L (0.0272 mg Cu/kg/day) versus ≥3 mg/L (0.0731 mg Cu/kg/day). No other differences between groups were found.

Table A-2. Incidence of Gastrointestinal Symptoms in Women Exposed to Copper in Drinking Water for 2-Week Periods

	Drinking water doses in mg Cu/kg/day			
Symptoms	0.0006 (control)	0.0272	0.0731	0.124
Abdominal pain only	2/60	1/60	3/60	2/60
Vomiting only	0/60	0/60	1/60	2/60
Nausea only	1/60	0/60	6/60	5/60
Total symptoms	3/60	1/60	10/60	9/60

Source: Pizarro et al. 1999

Selection of the Point of Departure for the MRL: The $BMDL_{10}$ of 0.055 mg/kg/day for gastrointestinal symptoms of abdominal pain, nausea, and vomiting in females was selected as the basis for the acute-duration oral MRL.

Incidence data for total gastrointestinal symptoms (abdominal pain, vomiting, and nausea, see Table A-2) were fit to all dichotomous models in EPA's Benchmark Dose Software (BMDS; version 3.3.2) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-values ($p \geq 0.1$), visual inspection of the dose-response curve, benchmark dose lower confidence limit (BMDL) <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. The dichotomous Hill model was recommended but was not selected, as the number of dose groups in the data should generally be at least one more than the number of parameters in a model. In this case, the dichotomous Hill model uses four parameters and the incidence data have four dose groups. The Multistage Degree 1 was the only viable alternative and the BMDL from this model was selected as the point of departure (POD). Table A-3 presents the benchmark dose (BMD) and BMDL values considered for MRL derivation, and Figure A-1 presents the curve from the chosen model.

Table A-3. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Women Following Exposure to Copper in Drinking Water Daily for 2 Weeks (Pizarro et al. 1999)

					Scaled residuals[c]	
Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Dose below BMD	Dose above BMD
Dichotomous Hill	0.051	0.032	0.29	145.93	-0.72	0.18
Gamma[d]			0.04	149.56	1.43	-0.63
Log-Logistic[e]			0.04	149.54	1.4	-0.62
Log-Probit[e]			0.09	147.62	1.60	-0.94
Multistage Degree 3[f]			0.03	149.87	1.39	-0.50
Multistage Degree 2[f]			0.03	149.87	1.39	0.50

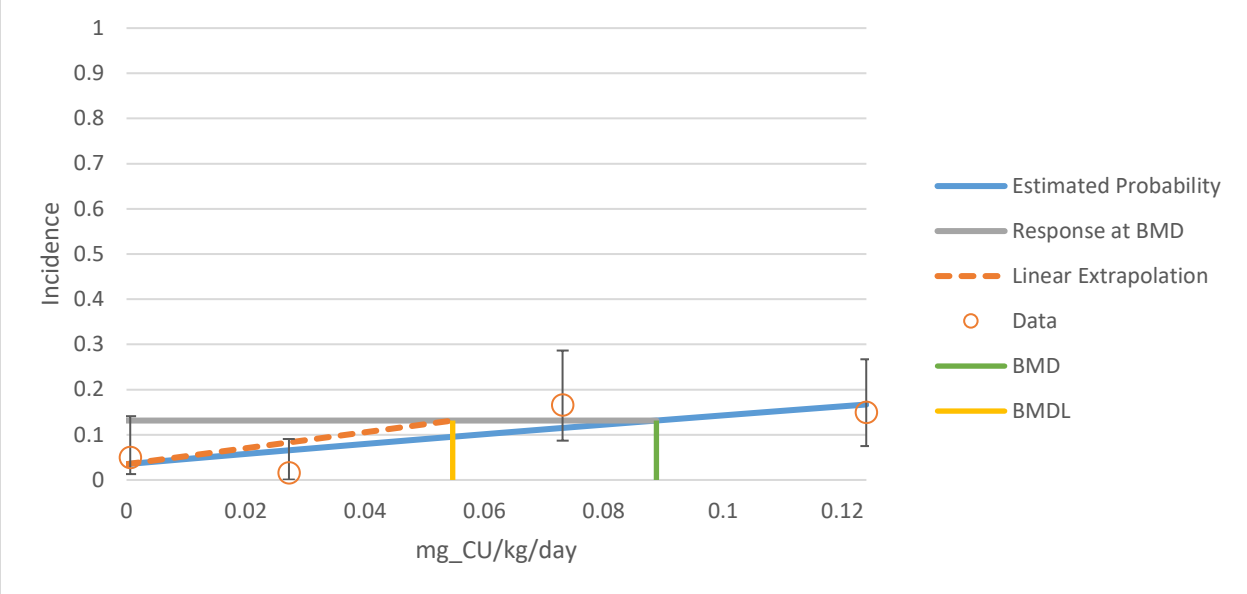
Table A-3. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Women Following Exposure to Copper in Drinking Water Daily for 2 Weeks (Pizarro et al. 1999)

Model	BMD_{10}[a] (mg/kg/day)	$BMDL_{10}$[a] (mg/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Multistage Degree 1[f,g]	**0.089**	**0.055**	**0.11**	**147.92**	**1.25**	-0.35
Weibull[d]			0.04	149.62	1.42	-0.60
Logistic			0.08	148.26	1.65	-0.58
Log-Probit			0.04	149.16	1.35	-0.67
Probit			0.09	148.1	1.58	-0.59
Quantal Linear	0.089	0.055	0.11	147.92	1.25	-0.35

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. Only the Multistage Degree 1, Quantal Linear, and Dichotomous Hill models provided adequate fit to the data. The dichotomous Hill model had the same number of parameters as the number of dose levels in the data; therefore, it was not selected. The Multistage Degree 1 and Quantal Linear models converged on the same form and this model was selected (Multistage Degree 1).

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Figure A-1. Fit of Frequentist Multistage Degree 1 Model to Data on Copper for Gastrointestinal Illness in Female Adults, Daily for 2 Weeks (Pizarro et al. 1999)



Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The $BMDL_{10}$ is divided by a total uncertainty factor of 3:

- 3 for human variability. A partial uncertainty factor for human variability was applied because the direct effects of copper on the gastrointestinal tract are unlikely to be substantially impacted by toxicokinetic differences among individuals. However, an uncertainty factor for human variability remains necessary because the principal study (Pizarro et al. 1999) was of healthy adult women, and there are some health conditions that may influence sensitivity to these effects. For example, health conditions that reduce the pH of gastric secretions (e.g., acute *H. pylori* infection, some neuroendocrine tumors or gastrinomas, rebound acid hypersecretion after stopping proton pump inhibitor therapy) may result in higher concentrations of free copper ions in contact with the gastrointestinal tract than those seen in healthy individuals at the same dose. In addition, health conditions that result in damage to the integrity of the gastrointestinal tract (ulcers, acid reflux) may also increase a person's sensitivity to oral copper exposure. The prevalence of these conditions is relatively high in the United States, so including an uncertainty factor of 3 for human variability is necessary to ensure that the MRL is adequately protective for these susceptible subpopulations.

$$MRL = \frac{BMDL_{10}}{UF} = \frac{0.055\ mg/kg/day}{3}$$

$$= 0.01833\ mg/kg/day\ (rounded\ to\ 0.02\ mg\ Cu/kg/day)$$

It should be noted that the acute-duration oral MRL may or may not be adequately protective for people with Wilson's disease, as the degree of protection will depend on their dietary and water intake levels as well as the degree to which their disease is medically controlled.

The acute-duration oral MRL of 0.02 mg Cu/kg/day reflects the intake of administered copper in addition to dietary background. The doses used in BMD modeling were doses of copper from copper sulfate solution provided to the participants in the study by Pizarro et al. (1999), whose average dietary copper intake was estimated[5] to be ~1.7 mg Cu/day or ~0.027 mg Cu/kg/day. This intake level is similar to estimates of dietary or dietary plus supplement copper intake in the United States (1.0–2.6 mg Cu/day; see Section 5.6, General Population Exposure).

Other Additional Studies or Pertinent Information that Lend Support to this MRL: In addition to the acute-duration controlled human exposure studies, there is an intermediate-duration controlled human exposure study that provides support for the critical effect (Araya et al. 2003b). The concentration-dependence of gastrointestinal symptoms was demonstrated in a study by Araya et al. (2003c), in which volunteers were exposed to the same copper dose in different volumes of water. The study authors observed a higher symptom frequency with higher copper concentrations (lower water volumes) when the intake (dose) was held constant. For example, a dose of 0.8 mg Cu administered in 100 mL of water induced nausea in 13% of subjects, while the same dose in 150 or 200 mL of water induced nausea in 9 and 7% of subjects, respectively (Araya et al. 2003c).

Histological changes in the gastrointestinal tract have been observed in experimental animal studies of intermediate duration, providing additional evidence for the gastrointestinal symptoms exhibited by

[5]For the four groups of subjects (receiving copper dosing in different sequences), Pizarro et al. (1999) reported average copper intakes of 1.4, 1.7, 1.8, and 1.9 mg Cu/day from food based on 24-hour diet recall. The average intake across groups was 1.725 mg Cu/day; this value was divided by the reported average body weight of 64 kg to estimate the dietary intake of 0.027 mg Cu/kg/day.

humans. In a combined repeat-dose and reproductive/developmental toxicity screening study of rats, significant increases in the incidence of squamous cell hyperplasia in the stomach were seen after 30–38 days of gavage exposure to doses ≥3 mg Cu/kg/day in females and ≥13 mg Cu/kg/day in males (Chung et al. 2009). NTP (1993) also observed increased incidences of squamous mucosa hyperplasia of forestomach in male and female rats at doses of 44–46 mg Cu/kg/day for 15 days and 33–34 mg Cu/kg/day for 13 weeks.

In animals exposed orally to copper for acute and intermediate durations, other effects (body weight, hepatic, renal, reproductive, and neurological) occurred at much higher doses (≥2 mg Cu/kg/day) (e.g., Al-Musawi et al. 2022; Guo et al. 2021; Husain et al. 2023; Kumar et al. 2019; Temiz et al. 2021).

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.02 mg/kg/day (adopted acute-duration MRL)
Critical Effect: See acute-duration oral MRL
Reference: Pizarro et al. 1999 (see acute-duration oral MRL)
Point of Departure: See acute-duration oral MRL
Uncertainty Factor: See acute-duration oral MRL
LSE Graph Key: 6
Species: Human

MRL Summary: The acute-duration oral MRL of 0.02 mg Cu/kg/day was adopted as the intermediate-duration oral MRL. The intermediate-duration database was assessed for suitability for MRL derivation, but the study with the lowest LOAEL (Araya et al. 2003b, 2004) yielded a higher BMDL (0.11 mg Cu/kg/day) for gastrointestinal symptoms in humans than the BMDL (0.055 mg Cu/kg/day for the same effect in humans; Pizarro et al. 1999) used as the POD for the acute-duration oral MRL. Additionally, the critical effect of gastrointestinal symptoms may result in part from a direct contact effect dependent on the concentration of copper present at a given time in the stomach rather than duration of exposure. Therefore, the acute-duration MRL is expected to be protective for intermediate-duration exposure scenarios.

Selection of the Critical Effect: See worksheet for acute-duration oral MRL.

Selection of the Principal Study: See worksheet for acute-duration oral MRL.

Summary of the Principal Study: See worksheet for acute-duration oral MRL.

Selection of the Point of Departure for the MRL: See worksheet for acute-duration oral MRL.

Calculations: See worksheet for acute-duration oral MRL.

Uncertainty Factor: See worksheet for acute-duration oral MRL.

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Gastrointestinal effects were recorded in a controlled experiment in humans exposed to copper in drinking water for 2 months (Araya et al. 2003b, 2004). In Araya et al. (2003b, 2004), significant increases in the proportion of subjects reporting at least one gastrointestinal symptom (nausea, vomiting, diarrhea, or abdominal pain) were seen at doses of 0.11 and 0.17 mg Cu/kg/day (corresponding to water concentrations of 4 and 6 mg Cu/L, respectively). A study in infants reported no increase in the reporting of gastrointestinal symptoms following daily exposure to doses up to 0.319 mg Cu/kg/day for 9 months (Olivares et al. 1998).

Histological changes in the gastrointestinal tract have been observed in experimental animal studies, providing additional evidence for the gastrointestinal symptoms exhibited by humans. In a combined repeat-dose and reproductive/developmental toxicity screening study of rats, significant increases in the incidence of squamous cell hyperplasia in the stomach were seen after 30–38 days of gavage exposure to

doses ≥3 mg Cu/kg/day in females and ≥13 mg Cu/kg/day in males (Chung et al. 2009). NTP (1993) also observed increased incidences of squamous mucosa hyperplasia of forestomach in male and female rats at doses of 44–46 mg Cu/kg/day for 15 days and 33–34 mg Cu/kg/day for 13 weeks.

As shown in Table A-4, animal studies of intermediate-duration oral exposure to copper have also identified hepatic, body weight, neurological, and reproductive system effects at doses ≥2.3 mg Cu/kg/day (Guo et al. 2021; Kline et al. 1971; Liu et al. 2020a, 2020b, 2021a, 2021b; Temiz et al. 2021).

Table A-4. Summary of Lowest LOAEL Values for Health Effects Following Intermediate-Duration Oral Exposure to Copper

Species (sex)	Frequency/ duration	NOAEL (mg Cu/kg/day)	LOAEL (mg Cu/kg/day)	Effect	Reference
Gastrointestinal effects					
Human; 1,365 adult men and women (mean ages 37–38 years)	2 months daily in water used for consumption, beverages, and soups	0.055 (2 mg Cu/L)	0.11 (4 mg Cu/L)	Increased incidence of gastrointestinal symptoms	Araya et al. 2003b, 2004
Human; 7 men and women (mean age 42 years)	12 weeks, daily by capsule	0.15	ND	No difference in gastrointestinal symptoms incidence	Pratt et al. 1985
Human; 80 exposed and 48 unexposed male and female infants	9 months (from 3 to 12 months of age) in water used for consumption and formula	0.319 (2 mg/L)	ND	No gastrointestinal symptoms observed	Olivares et al. 1998
Rat (F)	38 days Daily (gavage)	0.83	3	Increased incidence of squamous cell hyperplasia in the stomach	Chung et al. 2009
Body weight effects					
Pig (NS)	88 days (feed)	1.7	2.3	17% reduction in body weight gain	Kline et al. 1971
Mouse (M and F)	42 days daily (gavage)	ND	4	Terminal body weight decreased 15%	Liu et al. 2020a, 2020b, 2021a, 2021b
Neurological effects					
Rat (M)	16 weeks daily (gavage)	ND	2.6	Decreased locomotor activity and neuromuscular coordination, decreased passive avoidance response, less exploration time	Kumar et al. 2019

Table A-4. Summary of Lowest LOAEL Values for Health Effects Following Intermediate-Duration Oral Exposure to Copper

Species (sex)	Frequency/ duration	NOAEL (mg Cu/kg/day)	LOAEL (mg Cu/kg/day)	Effect	Reference
Hepatic effects					
Human; 11 men and 11 women (mean ages 33.5 and 29 years, respectively)	6 weeks, daily in food		ND	No effect on serum enzyme levels	O'Connor et al. 2003
Human; 7 men and women (mean age 42 years)	12 weeks, daily by capsule	0.15	ND	No effect on serum enzyme levels	Pratt et al. 1985
1,365 adult men and women (mean ages 37–38 years)	2 months daily in water used for consumption, beverages, and soups	0.17	ND	No effect on serum enzyme levels	Araya et al. 2003b, 2004
80 exposed and 48 unexposed male and female infants	9 months (from 3 to 12 months of age) in water used for consumption and formula	0.319	ND	No effect on serum bilirubin or AST, ALT, or GGT activities	Olivares et al. 1998
Rat (M)	28 days 2 times/week (gavage)	ND	3.9	Increased serum AST, ALT, and LDH centrilobular and vacuolar degeneration, dilatation of sinusoid, focal necrosis, and inflammatory cell infiltration in all or most animals	Temiz et al. 2021
Reproductive effects					
Mouse (M)	42 days daily (gavage)	ND	3.9	Increased sperm malformations and decreased sperm motility and concentration	Guo et al. 2021

ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female(s); GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified

The study by Araya et al. (2003b, 2004) identified the lowest NOAEL and corresponding LOAEL for adverse health outcomes (gastrointestinal symptoms) and was considered for possible use in deriving the intermediate-duration oral MRL. Araya et al. (2004) provided more detail on the copper dosing and gastrointestinal symptoms, so information from this publication was used. For groups given measured concentrations of 0.05, 2.02, 3.71, or 5.77 mg Cu/L in drinking water, corresponding daily copper intakes provided by Araya et al. (2004) were 0.08, 3.6, 6.9, and 11 mg/day, respectively. To calculate the dose, a

reference body weight of 65 kg for all adults (the midpoint between the default body weights for adult men [70 kg] and women [60 kg]) was used, resulting in doses of 0.001, 0.056, 0.11, and 0.17 mg Cu/kg/day. Incidences of at least one gastrointestinal symptom were 40/343, 50/327, 65/355, and 67/340 for the control through high dose groups, respectively (Araya et al. 2004).

BMD modeling was applied to the incidence data for gastrointestinal symptoms reported by Araya et al. (2004). The data were fit to all available dichotomous models in EPA's BMDS (version 3.3.2) using the extra risk option. Adequate model fit was judged by four criteria: chi-square goodness-of-fit p-values ($p \geq 0.1$), visual inspection of the dose-response curve, BMDL <10 times the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. Among the recommended, viable models providing adequate fit to the data, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was selected as the POD. The results of the BMD modeling for incidence of gastrointestinal symptoms in adults are presented in Table A-5.

Table A-5. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Adults Following Exposure to Copper in Drinking Water Daily for 2 Months (Araya et al. 2004)

Model	BMD_{10}[a] (mg Cu/kg/day)	$BMDL_{10}$[a] (mg Cu/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	0.26	0.059	NA	1,210.26	-0.000012	NR
Gamma[d]	0.18	0.12	0.84	1,206.62	-0.35	NR
Log-Logistic[e,f]	**0.18**	**0.11**	**0.86**	**1,206.56**	**-0.33**	**NR**
Log-Probit[e]	0.18	0.14	0.29	1,208.75	-0.57	NR
Multistage Degree 3[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Multistage Degree 2[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Multistage Degree 1[g]	0.18	0.12	0.84	1,206.62	-0.35	NR
Weibull[d]	0.18	0.12	0.84	1,206.62	-0.35	NR
Logistic	0.18	0.13	0.71	1,206.95	-0.40	NR
Log-Probit	0.19	0	0.81	1,208.32	-0.10	NR

Table A-5. Results from BMD Analysis of Incidence of Gastrointestinal Illness in Adults Following Exposure to Copper in Drinking Water Daily for 2 Months (Araya et al. 2004)

Model	BMD_{10}[a] (mg Cu/kg/day)	$BMDL_{10}$[a] (mg Cu/kg/day)	p-Value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Probit	0.18	0.13	0.73	1,206.90	-0.39	NR
Quantal Linear	0.18	0.12	0.84	1206.62	-0.35	NR

[a]BMDLs <10 times the lowest non-zero dose and their corresponding BMDs are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also, the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models provided adequate fit to the data (chi-square goodness-of-fit p-values ≥0.1). BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Log-Logistic).
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = benchmark dose (maximum likelihood estimate of the dose associated with the selected benchmark response); $BMDL_{10}$ = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); NR = BMD is higher than the highest dose tested; residual not available.

The selected model was the Log-Logistic model, which resulted in a BMDL of 0.11 mg Cu/kg/day. This BMDL is higher than the BMDL of 0.055 mg Cu/kg/day for same endpoint in the acute-duration human study by Pizarro et al. (1999) that was used as the POD for the acute-duration oral MRL. Therefore, ATSDR adopted the acute-duration oral MRL of 0.02 mg Cu/kg/day for intermediate-duration exposure. As noted previously, the critical effect of gastrointestinal symptoms may result from a direct contact effect that depends more on the concentration of copper present at a given time in the gastrointestinal system than on exposure duration. The concentration-dependence of gastrointestinal symptoms was demonstrated in a study by Araya et al. (2003c), in which volunteers were exposed to the same copper dose in different volumes of water. The study authors observed a higher symptom frequency with higher copper concentrations (lower water volumes) when the intake (dose) was held constant. For example, a dose of 0.8 mg copper administered in 100 mL of water induced nausea in 13% of subjects, while the same dose in 150 or 200 mL of water induced nausea in 9 and 7% of subjects, respectively (Araya et al. 2003c). Therefore, the acute-duration MRL is expected to be protective for intermediate-duration exposure scenarios.

Agency Contact (Chemical Managers): Breanna Alman, MPH

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Copper and compounds
CAS Numbers: 7440-50-8
Date: October 2024
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of chronic-duration oral MRL because available studies do not clearly identify the critical effects.

Rationale for Not Deriving an MRL: Human studies that met inclusion criteria did not provide sufficient dose-response information to examine the chronic-duration oral toxicity of copper. Two large prospective cohort studies used estimates of dietary copper intake based on food frequency questionnaires to examine associations with dementia (Wei et al. 2022, United States) and hypertension (He et al. 2022, China). Wei et al. (2022) estimated intake of copper from diet and supplements at enrollment in the cohort (1987–1989) and again a few years later (1993–1995) based on responses to a validated food frequency questionnaire administered by an interviewer. Subjects were followed for 20 years; an increase in dietary copper intake of 1 mg Cu/day was associated with increased risk of incident dementia. He et al. (2022) estimated dietary intake at baseline using three consecutive 24-hour recall surveys administered by a nutritionist, coupled with household food inventories on the same days; the participants were followed for a median duration of 6.1 years. Estimated copper intake ≥1.57 mg/day was associated with an increase in risk of incident hypertension (He et al. 2022). Both studies are limited because they do not account for either changes in diet over time or copper intake from water or local sources.

Three animal studies of chronic-duration oral exposure were located, but included only limited toxicological evaluations. One study in mice exposed for 850 days evaluated only survival and body weight and no other health outcomes (Massie and Aiello 1984). In the remaining two experiments, young or adult monkeys were exposed to copper in milk (young) or feed (both) for 3 years (Araya et al. 2012). These studies evaluated body weight, limited hematology and serum chemistry endpoints, and liver histopathology, and identified NOAELs of 5.5 and 7.5 mg Cu/kg/day (Araya et al. 2012). Neither the human studies nor the animal studies provide sufficient information to determine the critical effects of chronic-duration oral exposure to copper.

Agency Contact (Chemical Managers): Breanna Alman, MPH

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR COPPER

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to copper.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for copper. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of copper have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of copper are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for Copper released for public comment in 2022; thus, the literature search was restricted to studies published between January 2020 and October 2023. The following main databases were searched in October 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for copper. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to copper were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2023	((((("Copper/toxicity"[mh] OR "Copper/adverse effects"[mh] OR "Copper/poisoning"[mh] OR "Copper/pharmacokinetics"[mh]) OR ("Copper/blood"[mh] OR "Copper/cerebrospinal fluid"[mh] OR "Copper/urine"[mh]) OR ("Copper/antagonists and inhibitors"[mh]) OR ("Copper/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper sulfate/toxicity"[mh] OR "Copper sulfate/adverse effects"[mh] OR "Copper sulfate/poisoning"[mh] OR "Copper sulfate/pharmacokinetics"[mh]) OR ("Copper sulfate/blood"[mh] OR "Copper sulfate/cerebrospinal fluid"[mh] OR "Copper sulfate/urine"[mh]) OR ("Copper sulfate/antagonists and inhibitors"[mh]) OR ("Copper sulfate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper/pharmacology"[majr] OR "Copper sulfate/pharmacology"[majr]) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR (142-71-2[rn] OR 10380-28-6[rn]) OR (("Copper"[mh] OR "Copper Sulfate"[mh]) AND ((indexingmethod_automated OR indexingmethod_curated) AND ("RNA"[mh] OR "DNA"[mh] OR "DNA Replication"[mh] OR "Salmonella typhimurium"[mh] OR antagonist*[tw] OR inhibitor*[tw] OR "blood"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"serum"[tw] OR "plasma"[tw] OR pharmacokinetic*[tw] OR toxicokinetic*[tw] OR "pbpk"[tw] OR "poisoned"[tw] OR "poisoning"[tw] OR "urine"[tw] OR "urinary"[tw] OR "toxicity"[sh] OR "occupational diseases"[mh] OR "hazardous substances"[mh] OR "epidemiology"[sh] OR "epidemiologic studies"[mh])))) AND (2022/08/07:3000[mhda]))) OR (("Copper D-gluconate"[tiab] OR "Copper di-D-gluconate"[tiab] OR "Copper gluconate"[tiab] OR "Copper(2+) D-gluconate, (1:2)"[tiab] OR "Copper(2+) di(D-gluconate)"[tiab] OR "Copper(II)gluconate"[tiab] OR "Cupric gluconate"[tiab] OR "D-Gluconic acid, copper complex"[tiab] OR "D-Gluconic acid, copper salt"[tiab] OR "D-Gluconic acid, copper(2+) salt"[tiab] OR "Gluconic acid, copper salt, D-"[tiab] OR "Gluconic acid, copper(2+) salt"[tiab] OR "Helshas Cu"[tiab] OR "Labicuper"[tiab]) AND (2022/08/07:3000[edat] OR 2022/08/07:3000[crdat]))
	((((("Copper"[tw] OR "1721 Gold"[tw] OR "3EC-M3S-HTE"[tw] OR "3EC-M3VLP18"[tw] OR "ANAC 110"[tw] OR "ATS Adocopper IW"[tw] OR "BAC 13B-NK120"[tw] OR "Bronze powder"[tw] OR "C 100 (metal)"[tw] OR "C.I. 77400"[tw] OR "C.I. Pigment Metal 2"[tw] OR "Caswell No. 227"[tw] OR "CDA 101"[tw] OR "CDA 102"[tw] OR "CDA 110"[tw] OR "CDA 122"[tw] OR "CDX (metal)"[tw] OR "CE 1110"[tw] OR "CE 7 (metal)"[tw] OR "CF-T 8GD-SV"[tw] OR "CF-T 9A-HP-STD"[tw] OR "CF-T 9B-THE"[tw] OR "CF-T 9FZ-SV"[tw] OR "CFW 100-156"[tw] OR "CI 77400"[tw] OR "CI Pigment metal 2"[tw] OR "CU M3"[tw] OR "Cu-At-W 250"[tw] OR "Cubrotec 5000"[tw] OR "Cuivre metal"[tw] OR "Cutox 6010"[tw] OR "Cutox 6030"[tw] OR "DD Paste TH 9910"[tw] OR "Double Thin F-NP"[tw] OR "DT GLMP"[tw] OR "E 115 (metal)"[tw] OR "Gold bronze"[tw] OR "GT (metal)"[tw] OR "NDP-III"[tw] OR "NT-TAX-M"[tw] OR "NT-TAX-O"[tw] OR "OFHC Cu"[tw] OR "Paragard T 380a"[tw] OR "Paragard t380a"[tw] OR "Pigment metal 2"[tw] OR "Silcoat FCC-SP 99"[tw] OR "Tatum-T"[tw] OR "Unicoat 2845"[tw] OR "USLP-SE"[tw] OR "All Clear Root Destroyer"[tw] OR "Aqua Maid Permanent Algaecide"[tw] OR "Aquatronics Snail-A-Cide Dri-Pac Snail Powder"[tw] OR "Blue stone"[tw] OR "Blue vitriol"[tw] OR "Bonide Root Destroyer"[tw] OR "Cuivrol"[tw] OR "CuSO4"[tw] OR "Delcup"[tw] OR "EarthTec"[tw] OR "Hylinec"[tw] OR "Incracide 10A"[tw] OR "Incracide E 51"[tw] OR "MAC 570"[tw] OR "Monocopper sulfate"[tw] OR "Roman vitriol"[tw] OR "Trinagle"[tw] OR "CuCl2"[tw] OR "Eriocholcite"[tw] OR "cupric"[tw] OR "cuprous"[tw] OR ("cu"[tiab] NOT ("chronic urticaria"[tiab] OR "cognitively unimpaired"[tiab] OR "callous unemotional"[tiab] OR "cocaine users"[tiab]))) NOT medline[sb]) AND (2022/08/07:3000[edat] OR 2022/08/07:3000[crdat]))) AND (death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR "respiratory tract" OR "respiratory organ" OR "respiratory system" OR "respiratory volume" OR "respiratory function" OR "respiratory effect" OR "respiratory organ" OR "respiratory toxicity" OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR "cardiovascular system" OR "cardiovascular function" OR "cardiovascular effect" OR "cardiovascular organ" OR "cardiovascular toxicity" OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR

Table B-2. Database Query Strings

Database search date	Query string
	"digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR "renal system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR "dermal system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "dermal exposure" OR "dermal contact" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin acanthosis" OR "skin exposure" OR "skin contact" OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR "endocrine system" OR "endocrine function" OR "endocrine effect" OR "endocrine gland" OR "endocrine toxicity" OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action" OR "mechanism of absorption" OR "mechanism of distribution" OR "mechanism of excretion" OR "mechanism of metabolism" OR "mechanism of toxic effect" OR "adverse effect" OR "adverse effects" OR poisoning OR morbidity OR inflammation OR antagonist

Table B-2. Database Query Strings

Database search date	Query string
	OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish) ((("Copper/toxicity"[mh] OR "Copper/adverse effects"[mh] OR "Copper/poisoning"[mh] OR "Copper/pharmacokinetics"[mh]) OR ("Copper/blood"[mh] OR "Copper/cerebrospinal fluid"[mh] OR "Copper/urine"[mh]) OR ("Copper/antagonists and inhibitors"[mh]) OR ("Copper/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper sulfate/toxicity"[mh] OR "Copper sulfate/adverse effects"[mh] OR "Copper sulfate/poisoning"[mh] OR "Copper sulfate/pharmacokinetics"[mh]) OR ("Copper sulfate/blood"[mh] OR "Copper sulfate/cerebrospinal fluid"[mh] OR "Copper sulfate/urine"[mh]) OR ("Copper sulfate/antagonists and inhibitors"[mh]) OR ("Copper sulfate/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Copper/pharmacology"[majr] OR "Copper sulfate/pharmacology"[majr]) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("environmental exposure"[mh] OR ci[sh] OR toxicokinetics[mh:noexp])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR (("Copper"[mh] OR "Copper sulfate"[mh]) AND

Table B-2. Database Query Strings

Database search date	Query string
	(("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab])) OR ((10125-13-0[rn] OR 10257-54-2[rn] OR 1184-64-1[rn] OR 12019-06-6[rn] OR 12125-21-2[rn] OR 1317-38-0[rn] OR 1317-39-1[rn] OR 1344-67-8[rn] OR 1344-69-0[rn] OR 1344-70-3[rn] OR 17599-81-4[rn] OR 20427-59-2[rn] OR 527-09-3[rn] OR 7440-50-8[rn] OR 7447-39-4[rn] OR 7492-68-4[rn] OR 7758-89-6[rn] OR 7758-98-7[rn] OR 7758-99-8[rn] OR 82010-82-0[rn]) NOT ("Copper"[mh] OR "Copper Sulfate"[mh])) OR (142-71-2[rn] OR 10380-28-6[rn]) OR ("Copper D-gluconate"[tiab] OR "Copper di-D-gluconate"[tiab] OR "Copper gluconate"[tiab] OR "Copper(2+) D-gluconate, (1:2)"[tiab] OR "Copper(2+) di(D-gluconate)"[tiab] OR "Copper(II)gluconate"[tiab] OR "Cupric gluconate"[tiab] OR "D-Gluconic acid, copper complex"[tiab] OR "D-Gluconic acid, copper salt"[tiab] OR "D-Gluconic acid, copper(2+) salt"[tiab] OR "Gluconic acid, copper salt, D-"[tiab] OR "Gluconic acid, copper(2+) salt"[tiab] OR "Helshas Cu"[tiab] OR "Labicuper"[tiab])) AND (2020/01/01:3000[mhda] OR 2020/01/01:3000[edat] OR 2020/01/01:3000[crdat] OR 2020/01/01:3000[dp])) ((((("Copper"[tw] OR "1721 Gold"[tw] OR "3EC-M3S-HTE"[tw] OR "3EC-M3VLP18"[tw] OR "ANAC 110"[tw] OR "ATS Adocopper IW"[tw] OR "BAC 13B-NK120"[tw] OR "Bronze powder"[tw] OR "C 100 (metal)"[tw] OR "C.I. 77400"[tw] OR "C.I. Pigment Metal 2"[tw] OR "Caswell No. 227"[tw] OR "CDA 101"[tw] OR "CDA 102"[tw] OR "CDA 110"[tw] OR "CDA 122"[tw] OR "CDX (metal)"[tw] OR "CE 1110"[tw] OR "CE 7 (metal)"[tw] OR "CF-T 8GD-SV"[tw] OR "CF-T 9A-HP-STD"[tw] OR "CF-T 9B-THE"[tw] OR "CF-T 9FZ-SV"[tw] OR "CFW 100-156"[tw] OR "CI 77400"[tw] OR "CI Pigment metal 2"[tw] OR "CU M3"[tw] OR "Cu-At-W 250"[tw] OR "Cubrotec 5000"[tw] OR "Cuivre metal"[tw] OR "Cutox 6010"[tw] OR "Cutox 6030"[tw] OR "DD Paste TH 9910"[tw] OR "Double Thin F-NP"[tw] OR "DT GLMP"[tw] OR "E 115 (metal)"[tw] OR "Gold bronze"[tw] OR "GT (metal)"[tw] OR "NDP-III"[tw] OR "NT-TAX-M"[tw] OR "NT-TAX-O"[tw] OR "OFHC Cu"[tw] OR "Paragard T 380a"[tw] OR "Paragard t380a"[tw] OR "Pigment metal 2"[tw] OR "Silcoat FCC-SP 99"[tw] OR "Tatum-T"[tw] OR "Unicoat 2845"[tw] OR "USLP-SE"[tw] OR "All Clear Root Destroyer"[tw] OR "Aqua Maid Permanent Algaecide"[tw] OR "Aquatronics Snail-A-Cide Dri-Pac Snail Powder"[tw] OR "Blue stone"[tw] OR "Blue vitriol"[tw] OR "Bonide Root Destroyer"[tw] OR "Cuivrol"[tw] OR "CuSO4"[tw] OR "Delcup"[tw] OR "EarthTec"[tw] OR "Hylinec"[tw] OR "Incracide 10A"[tw] OR "Incracide E 51"[tw] OR "MAC 570"[tw] OR "Monocopper sulfate"[tw] OR "Roman vitriol"[tw] OR "Trinagle"[tw] OR "CuCl2"[tw] OR "Eriocholcite"[tw] OR "cupric"[tw] OR "cuprous"[tw] OR ("cu"[tiab] NOT ("chronic urticaria"[tiab] OR "cognitively unimpaired"[tiab] OR "callous unemotional"[tiab] OR "cocaine users"[tiab]))) NOT medline[sb]) AND (2020/01/01:3000[edat] OR 2020/01/01:3000[crdat] OR 2020/01/01:3000[dp]))) AND (death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR "respiratory tract" OR "respiratory organ" OR "respiratory system" OR "respiratory volume" OR "respiratory function" OR "respiratory effect" OR "respiratory organ" OR "respiratory toxicity" OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR trachea OR tracheobronchial OR lung OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR

Table B-2. Database Query Strings

Database search date	Query string
	laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR "cardiovascular system" OR "cardiovascular function" OR "cardiovascular effect" OR "cardiovascular organ" OR "cardiovascular toxicity" OR "circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal OR "digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "gi tract" OR "gi disorder" OR abdominal OR esophagus OR stomach OR intestine OR pancreas OR pancreatic OR diarrhea OR nausea OR vomit OR ulcer OR constipation OR emesis OR "gut microbes" OR "gut flora" OR "gut microflora" OR anorexia OR hematological OR hematology OR hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR "renal system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR bun OR nephropathy OR nephrotox* OR "dermal system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "dermal exposure" OR "dermal contact" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin acanthosis" OR "skin exposure" OR "skin contact" OR dermatitis OR psoriasis OR edema OR ulceration OR acne OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR "endocrine system" OR "endocrine function" OR "endocrine effect" OR "endocrine gland" OR "endocrine toxicity" OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* OR cognitive OR vertigo OR drowsiness OR headache OR ataxia OR reproductive OR "reproduction system" OR "reproduction function" OR "reproduction effect" OR "reproduction toxicity" OR fertility OR "maternal toxicity" OR developmental OR "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR

Table B-2. Database Query Strings

Database search date	Query string
	"altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action" OR "mechanism of absorption" OR "mechanism of distribution" OR "mechanism of excretion" OR "mechanism of metabolism" OR "mechanism of toxic effect" OR "adverse effect" OR "adverse effects" OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR medaka OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR wistar OR wood-mouse OR zebra-fish OR zebrafish)
NTRL	
10/2023	Date Published 2019 to 2023, Title or Keyword field copper OR cupric OR cuprous
Toxcenter	
10/2023	FILE 'TOXCENTER' ENTERED AT 10:39:30 ON 04 OCT 2023 L1 325170 SEA 7440-50-8 L2 22300 SEA 10125-13-0 OR 10257-54-2 OR 10380-28-6 OR 1184-64-1 OR 12019-06-6 OR 12125-21-2 OR 13005-35-1 OR 1317-38-0 OR 1317-39-1 OR 1344-67-8 OR 1344-69-0 L3 39282 SEA 1344-70-3 OR 142-71-2 OR 17599-81-4 OR 20427-59-2 OR 4180-12-5 OR 527-09-3 OR 7447-39-4 OR 7492-68-4 OR 7758-89-6 OR 7758-98-7 OR 7758-99-8 OR 82010-82-0 L4 366811 SEA L1 OR L2 OR L3 L5 304934 SEA L4 NOT PATENT/DT L6 17407 SEA L5 AND ED>=20220804 L7 17376 SEA L6 AND PY>2018

Table B-2. Database Query Strings

Database search date	Query string
	ACT TOXQUERY/Q

	L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L23 QUE (ENDOCRIN? AND DISRUPT?)
	L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L30 QUE (NEPHROTOX? OR HEPATOTOX?)
	L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L33 QUE L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25

Table B-2. Database Query Strings

Database search date	Query string
	OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 L34 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L36 QUE L33 OR L34 OR L35 L37 QUE (NONHUMAN MAMMALS)/ORGN L38 QUE L36 OR L37 --------- L50 7690 SEA L7 AND L38 L51 871 SEA L50 AND MEDLINE/FS L52 1312 SEA L50 AND BIOSIS/FS L53 2026 DUP REM L51 L52 (157 DUPLICATES REMOVED) L*** DEL 871 S L50 AND MEDLINE/FS L*** DEL 871 S L50 AND MEDLINE/FS L54 867 SEA L53 L*** DEL 1312 S L50 AND BIOSIS/FS L*** DEL 1312 S L50 AND BIOSIS/FS L55 1159 SEA L53 L56 1159 SEA (L54 OR L55) AND BIOSIS/FS D SCAN L56 Limited to py 2019-present and entry date 7/2019-present FILE 'TOXCENTER' ENTERED AT 09:41:02 ON 04 AUG 2022 CHARGED TO COST=EH038.08.02.LB.04 DIS SAVED ACT COPPER/A --------- L1 (306093)SEA FILE=TOXCENTER 7440-50-8 L2 (19689)SEA FILE=TOXCENTER 10125-13-0 OR 10257-54-2 OR 10380-28-6 OR 1184-64-1 OR 12019-06-6 OR 12125-21-2 OR 13005-35-1 OR 1317-38-0 OR 1317-39-1 OR 1344-67-8 OR 1344-69-0 L3 (35864)SEA FILE=TOXCENTER 1344-70-3 OR 142-71-2 OR 17599-81-4 OR 20427-59-2 OR 4180-12-5 OR 527-09-3 OR 7447-39-4 OR 7492-68-4 OR 7758-89-6 OR 7758-98-7 OR 7758-99-8 OR 82010-82-0 L4 (343873)SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 (50997)SEA FILE=TOXCENTER L4 AND ED>=20190701 L6 (42493)SEA FILE=TOXCENTER L5 NOT PATENT/DT L7 (42493)SEA FILE=TOXCENTER L6 NOT TSCATS/FS L8 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L9 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L10 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)

Table B-2. Database Query Strings

Database search date	Query string
	L11 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L12 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L20 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L21 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L22 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L23 QUE (ENDOCRIN? AND DISRUPT?) L24 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L25 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L26 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L27 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L28 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L29 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L30 QUE (NEPHROTOX? OR HEPATOTOX?) L31 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L32 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L33 QUE L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 L34 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L35 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE L33 OR L34 OR L35 L37 QUE (NONHUMAN MAMMALS)/ORGN L38 QUE L36 OR L37 L39 (18027)SEA FILE=TOXCENTER L7 AND L38 L40 (17269)SEA FILE=TOXCENTER L39 AND PY>2018 L41 (2479)SEA FILE=TOXCENTER L40 AND MEDLINE/FS L42 (3474)SEA FILE=TOXCENTER L40 AND BIOSIS/FS L43 (11296)SEA FILE=TOXCENTER L40 AND CAPLUS/FS L44 (20)SEA FILE=TOXCENTER L40 NOT (L41 OR L42 OR L43) L45 (15088)DUP REM L41 L42 L44 L43 (2181 DUPLICATES REMOVED) L46 (2478)SEA FILE=TOXCENTER L45 L47 (3082)SEA FILE=TOXCENTER L45 L48 (9510)SEA FILE=TOXCENTER L45 L49 (18)SEA FILE=TOXCENTER L45 L50 12610 SEA FILE=TOXCENTER (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS --------- L51 3082 SEA FILE=TOXCENTER L50 AND BIOSIS/FS

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2023	Compounds searched: 7440-50-8; 7758-98-7; 7758-99-8; 10257-54-2; 17599-81-4; 7447-39-4; 1344-67-8; 7758-89-6; 10125-13-0; 1317-39-1; 1317-38-0; 1344-70-3; 12019-06-6; 82010-82-0; 527-09-3; 13005-35-1; 4180-12-5; 142-71-2; 1344-69-0; 12125-21-2; 20427-59-2; 1184-64-1; 7492-68-4; 10380-28-6
NTP	
10/2023	Limited 2010-present "copper" "cupric" "cuprous"
Regulations.gov	
10/2023	Limited to 2019–present copper cupric cuprous
NPIRS	
1/2024	SEARCH CRITERIA Active Ingredient: Copper as elemental (CAS #: 7440-50-8) (PC Code: 22501), Copper carbonate hydroxide (CAS #: 1184-64-1) (PC Code: 22901), Copper hydroxide (CAS #: 20427-59-2) (PC Code: 23401), Copper sulfate pentahydrate (CAS #: 7758-99-8) (PC Code: 24401), Copper sulfate monohydrate (CAS #: 10257-54-2) (PC Code: 24402), Copper sulfate (anhydrous) (CAS #: 7758-98-7) (PC Code: 24408), Copper oxide, black (CAS #: 1317-38-0) (PC Code: 42401), Copper 8-hydroxyquinoline (CAS #: 10380-28-6) (PC Code: 24002), Copper oxide (Cu2O) (CAS #: 1317-39-1) (PC Code: 25601), Cuprous and cupric oxide, mixed (CAS #: 82010-82-0) (PC Code: 42403)

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Submission Date Start: 2014-01-01
NIH RePORTER	
10/2023	Search Criteria Fiscal Year: Active Projects Text Search: "copper" OR "cupric" OR "cuprous" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 15,262
- Number of records identified from other strategies: 183
- Total number of records to undergo literature screening: 15,445

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on copper:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

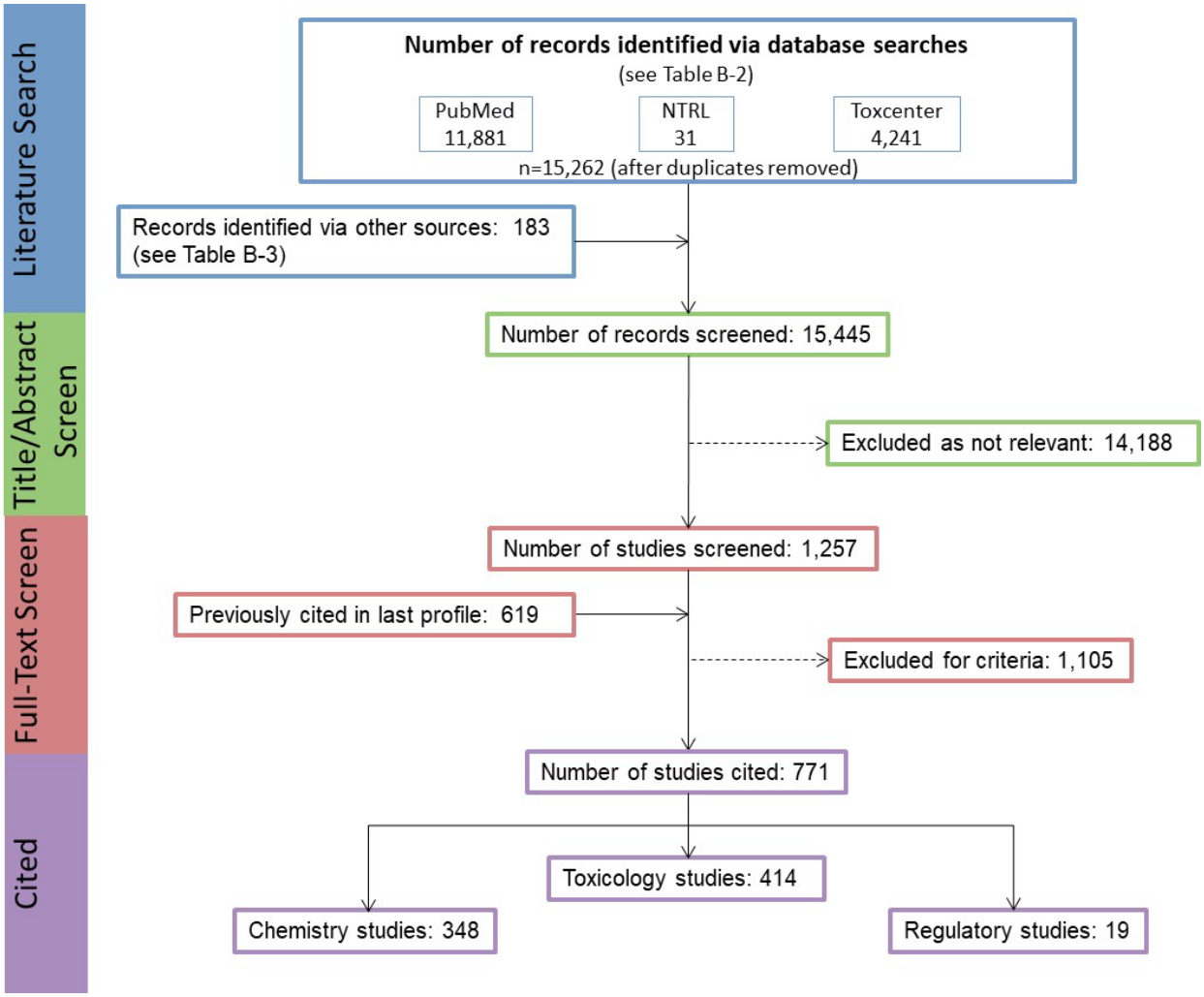
- Number of titles and abstracts screened: 15,445
- Number of studies considered relevant and moved to the next step: 1,257

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,257
- Number of studies cited in the pre-public draft of the toxicological profile: 619
- Total number of studies cited in the profile: 771

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. October 2023 Literature Search Results and Screen for Copper



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR COPPER

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to copper, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to copper:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to copper. The inclusion criteria used to identify relevant studies examining the health effects of copper are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of copper. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the Draft Toxicological Profile for Copper released for public comment in 2022. See Appendix B for the databases searched and the search strategy.

A total of 15,445 records relevant to all sections of the toxicological profile were identified in the literature search (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of copper.

Title and Abstract Screen. In the Title and Abstract Screen step, 15,445 records were reviewed; 56 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 174 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 174 documents (181 studies), 57 documents (61 studies) were included in the qualitative review.

There are extensive databases of human and animal data pertaining to copper, but the quality of the data varies widely. Studies were selected for inclusion in the toxicological profile if they provided adequate information for hazard identification and/or dose-response assessment. Basic study quality criteria were

developed for epidemiological data and for animal studies using oral administration. These criteria were applied to the studies included after full-text screening, and only studies meeting these criteria were considered in the toxicological profile. There were few animal studies of inhalation exposure to copper, so all studies identified were included.

A priori Study Quality Screen for Human Studies. Several hundred human studies were identified in the literature searches. Copper is an essential mineral that occurs naturally in food and water, and humans are exposed to a range of baseline copper doses from these sources. Therefore, the most reliable hazard identification and dose-response information from human studies comes from studies of controlled exposure and/or studies of clearly elevated exposures (e.g., occupational settings where copper is the primary exposure). For this toxicological profile, all human controlled exposure studies examining health outcomes (not mechanistic endpoints) were included. Case reports and case series, while not epidemiological studies, were included in the assessment if there was clear evidence of excess exposure to copper.

For the updated profile, studies of occupational settings were included if:

- Copper was the primary exposure (by exposure concentration or industrial activity, such as copper smelting) or one of few constituents of the exposure mix were included, and exposure measures (air concentrations or biomarkers) demonstrated a differential copper exposure between groups. Examples of studies excluded by this criterion include studies of manganese workers (Ge et al. 2020, 2021, 2022), rare earth miners (Liu et al. 2021c), automotive technicians (Akinwande et al. 2021), and refinery workers (Ajeel et al. 2021).
- The referent group had lower or no exposure to copper or other heavy metals. For example, two studies (Haase et al. 2021, 2022) were excluded because the referent group used in these studies was exposed to lead dust and dust of precious metals.

After applying the criteria, four occupational studies were selected for inclusion.

Studies of populations without quantified exposure to exogenous copper were excluded. Many studies examined associations between various health outcomes and copper concentrations in urine, serum/blood, hair, nails, or other physiological fluids or tissues in the general population. These studies did not distinguish between conditions of copper deficiency, adequacy, and excess, and as such, do not inform hazard identification. In addition, perturbation of copper homeostasis may result from various health conditions, leading to the potential for reverse causation or confounding in these studies.

For the updated profile, human epidemiological studies of the general population (non-occupational settings) were included if they met the following criteria:

- Copper concentration in food, water, or air was measured or estimated for individual subjects in the study (e.g., ecological study designs were not included).
- Exposure was not measured after outcome.
- The statistical analysis of the association considered at least one potential covariate. Studies limited to bivariate analyses (i.e., Pearson or Spearman correlation coefficients), or analyses limited to comparison between copper concentrations/biomarkers in cases and controls were not included.

Applying the criteria above resulted in the selection of 11 studies of general population exposure.

A priori Study Quality Screen for Animal Studies using Oral Administration. Among animal toxicity studies using oral administration identified in the literature searches, the quality of the studies varied widely. For example, some studies did not report the form of copper administered, some reported the

dose or concentration inconsistently, and some did not clearly distinguish between mg/kg body weight and mg/kg diet. Many studies administered copper in diet or drinking water without reporting intake levels. Water intake (but not dietary intake) was shown to decrease with increasing copper concentration (NTP 1993), so reference intake rates may overestimate the dose of copper from drinking water studies.

Of the animal studies using oral administration, studies were included in the profile if:

- The form of copper (compound) administered was clearly reported.
- The concentration(s) or dose(s) were consistently reported as either the compound (e.g., mg $CuSO_4$/kg) or as copper (mg Cu/kg).
- When reported as mg/kg, the study clearly reported the value as mg/kg body weight or mg/kg diet.
- The dose of copper or copper compound administered was reported or could be reliably estimated. Studies that used drinking water administration but did not provide water intake information were not included.
- Additionally, a number of studies examined animals with genetic defects similar to Wilson's disease (e.g., Long-Evans Cinnamon rats and Bedlington terrier dogs) were not included.

Applying these criteria resulted in the selection of 82 animal oral toxicity studies for inclusion in the toxicological profile.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)

Table C-2. Data Extracted From Individual Studies

No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Documents for copper and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2–2.19 of the profile and in the Levels of Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for copper identified in human and animal studies are presented in Table C-3 and C-4, respectively. The available human toxicity studies primarily evaluated the gastrointestinal endpoint including in controlled-exposure studies. Observational and controlled-exposure cohort studies and population level studies have examined a wide range of endpoints in humans. Animal studies examined all endpoints following oral exposure to copper. A very limited number of animal studies examined toxicity following inhalation exposure. Gastrointestinal and hepatic effects were considered sensitive outcomes of oral copper exposure, as effects were observed at low doses in humans and animals and are commonly reported in case reports of human exposures. Respiratory effects were considered a sensitive outcome of inhalation copper exposure because they were seen at low exposure levels in animals and reported in some occupational studies of inhalation exposure. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. Case reports and case series, as well as community and occupational health investigations that did not include referent groups, were not included in the formal systematic review due to inherent high risk of bias and low confidence based on study design. However, consistent findings from these studies were considered during the adjustment of the confidence rating (with regards to consistency and/or severity of observed effects). There were 61 studies (published in 57 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Copper Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other noncancer	Cancer
Inhalation Studies																	
Cohort		3 1	2 1									1 1					1 1
Case Control												1 1			1 0		
Population		5 4	2 2	1 1	1 1		1 1		1 1	1 1	1 1		1 1	1 1		2 2	
Case Series		8 8		1 1	1 1		1 1	1 1					1 1				
Oral Studies																	
Cohort			1 1	1 0									1 1				
Case Control	2 0		1 0	9 8	2 0		7 0					1 1	1 1				
Population			3 0	1 0	2 2		1 0						2 1			1 0	
Case Series		9 9	10 10	15 15	20 20	2 2	19 19	19 19	6 6		3 3	2 2	4 4				
Dermal Studies																	
Cohort																	
Case Control																	
Population																	
Case Series					1 1		1 1		2 2			4 4					

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

APPENDIX C

Table C-4. Overview of the Health Outcomes for Copper Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other noncancer	Cancer
Inhalation Studies																	
Acute-duration		4 3										2 2					
Intermediate-duration	1 0	3 1			1 0		1 0	1 0				1 0	1 0				
Chronic-duration																	
Oral Studies																	
Acute-duration	1 1		1 1	2 2			4 4	4 3						6 4	1 0		
Intermediate-duration	31 17	8 1	10 3	7 5	10 8	2 1	27 19	16 12			6 0	6 3	17 11	22 16	5 3	1 1	
Chronic-duration	2 0				1 1		1 0										
Dermal Studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

For the copper profile, the OHAT guidance on the question "Is there confidence in the exposure characterization?" was interpreted to only detract modestly from the rating in consideration of reporting of copper purity in studies. Studies were rated as probably low risk of bias (+) on this question if purity was not reported but the study does report that the test article was obtained from a commercial supplier of research chemicals, and if there is nothing in the study suggesting a risk of the test article decomposition during dosing or storage.

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of copper health effects studies (observational epidemiology, and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Copper—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?*	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Gastrointestinal effects							
Cohort studies							
Buchanan et al. 1999	+	+	–	–	–	++	Second
Pettersson et al. 2003	++	+	+	+	+	++	First
Case-control studies							
Buchanan et al. 1999	+	+	++	+	+	++	First
Outcome: Hepatic effects (no studies)							
Outcome: Respiratory effects							
Cohort studies							
Boogaard et al. 2013	++	+	–	–	++	++	Second
Gehring et al. 2015	++	+	+	–	+	++	First
Yu et al. 2021b	++	+	+	–	+	++	First

Table C-8. Summary of Risk of Bias Assessment for Copper—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Cross-sectional studies							
Fouad and Ramadan 2022	+	–	+	–	+	++	Second
Saadiani et al. 2023	+	–	+	–	+	++	Second
Mourad and El-Sherif 2022	+	–	+	–	–	++	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Copper–Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Gastrointestinal effects (oral only)								
Oral acute exposure								
Araya et al. 2001	++	++	++	+	+	+	++	First
Araya et al. 2003a	++	++	++	++	+	+	++	First
Araya et al. 2003c	++	++	++	+	+	+	++	First
Gotteland et al. 2001	++	++	++	++	–	+	++	First
Olivares et al. 2001	+	+	+	+	–	+	++	First
Pizarro et al. 1999	++	++	++	++	+	+	++	First
Pizarro et al. 2001	++	++	++	++	–	+	++	First
Oral intermediate exposure								
Araya et al. 2003b, 2004	++	++	++	++	–	+	++	First
Olivares et al. 1998	–	–	+	+	–	–	++	Second
Pratt et al. 1985	+	++	++	+	–	–	–	Second
Outcome: Hepatic effects (oral only)								
Oral acute exposure								
Pizarro et al. 1999	++	++	++	++	+	+	++	First
Pizarro et al. 2001	++	++	++	+	–	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Copper–Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings							
	Selection bias		Performance bias	Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Oral intermediate exposure								
Araya et al. 2003b, 2004	++	++	++	++	–	+	++	First
O'Connor et al. 2003	++	++	++	++	–	+	++	First
Olivares et al. 1998	–	–	+	+	–	–	++	Second
Pratt et al. 1985	+	++	++	+	–	–	–	Second
Rojas-Sobarzo et al. 2013	++	++	++	+	++	+	++	First
Outcome: Respiratory effects (no studies)								

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	Risk of bias tier
Outcome: Gastrointestinal effects (oral only)									
Oral acute exposure									
Husain et al. 2021 (rat)	–	+	+	+	+	–	+	+	First
Yamamoto et al. 2004 (shrew)	–	+	+	+	–	–	++	++	First
Oral intermediate exposure									
Chung et al. 2009 (rat)	+	+	+	+	+	–	+	+	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 13 weeks, feed)	+	+	++	+	++	++	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Hepatic effects									
Inhalation acute exposure									
Poland et al. 2022 (rat, sulfate)	++	+	+	+	++	++	++	++	First
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Oral acute exposure									
Alhusaini et al. 2018a (rat)	+	+	–	–	++	+	+	++	First
Alhusaini et al. 2018b (rat)	–	+	–	–	++	+	+	++	First
Haywood 1980 (rat)	–	+	+	+	+	–	+	+	First
Haywood and Comerford 1980 (rat)	–	+	+	+	++	–	+	+	First
Oral intermediate exposure									
Abe et al. 2008 (rat)	+	+	++	–	+	+	+	++	First
Adele et al. 2023 (rat)	–	+	–	+	++	–	+	+	First
Chung et al. 2009 (rat)	+	+	+	+	+	+	+	+	First

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Dab et al. 2023 (mouse)	–	+	+	+	++	+	+	+	First
Epstein et al. 1982 (rat)	+	+	++	–	++	–	++	++	First
Fuentealba et al. 2000 (rat)	–	+	–	+	+	–	+	–	Second
Haywood 1980 (rat)	–	+	+	+	+	–	+	+	First
Haywood and Comerford 1980 (rat)	–	+	+	+	++	–	+	+	First
Haywood and Loughran 1985 (rat)	–	+	+	+	+	– –	+	+	First
Kumar et al. 2015, 2016a, 2016b (rat)	+	+	++	+	+	+	++	++	First
Kumar and Sharma 1987 (rat)	+	+	–	+	– –	–	+	++	First
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	+	+	+	+	+	–	+	–	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
NTP 1993 (rat, 15 days, water)	+	+	++	+	–	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat,13 weeks, feed)	+	+	++	+	++	++	++	++	First
Patwa and Flora 2020 (rat)	–	+	–	+	++	+	+	+	First
Rana and Kumar 1980 (rat)	– –	+	–	–	–	–	+	++	Second
Sakhaee et al. 2012 (rat)	+	+	++	–	+	–	+	++	First
Sakhaee et al. 2014 (mouse)	+	+	++	+	+	–	+	++	First
Seven et al. 2018 (rat)	+	+	–	–	+	+	+	++	First
Sugawara et al. 1995 (rat)	+	+	+	+	++	– –	+	+	First
Suttle and Mills 1966 (pig, Experiment 1)	++	+	++	+	++	–	++	++	First
Suttle and Mills 1966 (pig, Experiment 2)	++	+	++	+	++	–	++	++	First

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Temiz et al. 2021 (rat)	+	+	–	+	++	–	+	+	First
Wu et al. 2020 (mouse)	–	+	++	–	++	+	+	++	First
Yu et al. 2021a (rat)	+	+	–	+	+	– –	+	+	First
Zhang et al. 2020 (pig)	+	+	+	+	+	–	+	+	First
Oral chronic exposure									
Araya et al. 2012 (monkey)	+	+	+	–	++	–	+	++	First
Outcome: Respiratory effects									
Inhalation acute exposure									
Poland et al. 2022 (rat, sulfate)	++	+	+	+	++	++	++	++	First
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Inhalation intermediate exposure									
Poland et al. 2022 (rat, oxide)	++	+	+	+	++	++	++	++	First
Johansson et al. 1983 (rabbit)	+	+	+	+	+	–	+	+	First
Johansson et al. 1984 (rabbit)	+	+	+	+	+	–	+	+	First

Table C-10. Summary of Risk Bias Assessment for Copper–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Oral intermediate exposure									
Chung et al. 2009 (rat)	+	+	+	+	+	+	+	+	First
Draper et al. 2023 (rat)	++	+	++	+	++	++	++	+	First
NTP 1993 (mouse, 15 days, water)	+	+	++	+	+	++	++	++	First
NTP 1993 (mouse, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat, 15 days, water)	+	+	++	+	+	++	++	++	First
NTP 1993 (rat, 15 days, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (mouse, 13 weeks, feed)	+	+	++	+	++	++	++	++	First
NTP 1993 (rat,13 weeks, feed)	+	+	++	+	++	++	++	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to copper and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to copper and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes."
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes."
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes."
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes."

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining gastrointestinal and neurological health effects observed in the observational epidemiology, controlled-exposure human studies and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence.

Table C-14. Presence of Key Features of Study Design for Copper—Observational Epidemiology Studies

Reference	Key features: Controlled Exposure	Exposure prior to outcome	Outcome assess on individual level	Comparison group	Initial study confidence
Outcome: Gastrointestinal effects					
Cohort studies					
Buchanan et al. 1999	No	Yes	Yes	Yes	Moderate
Pettersson et al. 2003	No	Yes	Yes	Yes	Moderate
Case-control studies					
Buchanan et al. 1999	No	Yes	Yes	Yes	Moderate
Outcome: Hepatic effects (no studies)					
Outcome: Respiratory effects					
Cohort studies					
Boogaard et al. 2013	No	Yes	Yes	Yes	Moderate
Gehring et al. 2015	No	Yes	Yes	Yes	Moderate
Yu et al. 2021b	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Fouad and Ramadan 2022	No	Yes	Yes	Yes	Moderate
Saadiani et al. 2023	No	Yes	Yes	Yes	Moderate
Mourad and El-Sherif 2022	No	Yes	Yes	Yes	Moderate

Table C-15. Presence of Key Features of Study Design for Copper–Human-Controlled Exposure Studies

Reference	Key feature: Concurrent Control Group	Sufficient number of subjects per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Gastrointestinal effects					
Oral acute exposure					
Araya et al. 2001	Yes	Yes	Yes	Yes	High
Araya et al. 2003a	Yes	Yes	Yes	Yes	High
Araya et al. 2003c	Yes	Yes	Yes	Yes	High
Gotteland et al. 2001	Yes	Yes	Yes	Yes	High

Table C-15. Presence of Key Features of Study Design for Copper–Human-Controlled Exposure Studies

Reference	Key feature: Concurrent Control Group	Key feature: Sufficient number of subjects per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Olivares et al. 2001	Yes	Yes	Yes	Yes	High
Pizarro et al. 1999	Yes	Yes	Yes	Yes	High
Pizarro et al. 2001	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Araya et al. 2003b, 2004	Yes	Yes	Yes	Yes	High
Olivares et al. 1998	Yes	Yes	Yes	Yes	High
Pratt et al. 1985	Yes	No	No	No	Very Low
Outcome: Hepatic effects					
Oral acute exposure					
Pizarro et al. 1999	Yes	Yes	No	Yes	Moderate
Pizarro et al. 2001	Yes	Yes	No	Yes	Moderate
Oral intermediate exposure					
Araya et al. 2003b, 2004	Yes	Yes	No	Yes	Moderate
O'Connor et al. 2003	Yes	Yes	No	Yes	Moderate
Olivares et al. 1998	Yes	Yes	No	Yes	Moderate
Pratt et al. 1985	Yes	No	No	No	Very Low
Rojas-Sobarzo et al. 2013	Yes	Yes	No	Yes	Moderate
Outcome: Respiratory effects (no studies)					

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Gastrointestinal effects					
Oral acute exposure					
Husain et al. 2021 (rat)	Yes	No	Yes	No	Low
Yamamoto et al. 2004 (shrew)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Chung et al. 2009 (rat)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat,13 weeks, feed)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation acute exposure					
Poland et al. 2022 (rat, sulfate)	Yes	No	No	No	Very Low
Poland et al. 2022 (rat, oxide)	Yes	No	No	No	Very Low
Inhalation intermediate exposure					
Poland et al. 2022 (rat, oxide)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Alhusaini et al. 2018a (rat)	Yes	No	Yes	Yes	Moderate
Alhusaini et al. 2018b (rat)	Yes	No	Yes	Yes	Moderate
Haywood 1980 (rat)	Yes	No	Yes	No	Low
Haywood and Comerford 1980 (rat)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Abe et al. 2008 (rat)	Yes	No	Yes	Yes	Moderate
Adele et al. 2023 (rat)	Yes	No	No	Yes	Low
Chung et al. 2009 (rat)	Yes	Yes	Yes	No	Moderate
Dab et al. 2023 (mouse)	Yes	No	No	Yes	Low

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Epstein et al. 1982 (rat)	Yes	No	Yes	Yes	Moderate
Fuentealba et al. 2000 (rat)	Yes	No	Yes	No	Low
Haywood 1980 (rat)	Yes	No	Yes	No	Low
Haywood and Comerford 1980 (rat)	Yes	No	No	Yes	Low
Haywood and Loughran 1985 (rat)	Yes	Yes	Yes	No	Moderate
Kumar et al. 2015, 2016a, 2016b (rat)	Yes	Yes	Yes	Yes	High
Kumar and Sharma 1987 (rat)	Yes	Yes	No	No	Low
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	Yes	No	Yes	No	Low
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat,13 weeks, feed)	Yes	Yes	Yes	Yes	High
Patwa and Flora 2020 (rat)	Yes	No	Yes	Yes	Moderate
Rana and Kumar 1980 (rat)	Yes	Yes	Yes	Yes	High
Sakhaee et al. 2012 (rat)	Yes	Yes	Yes	Yes	High
Sakhaee et al. 2014 (mouse)	Yes	Yes	No	Yes	Moderate
Seven et al. 2018 (rat)	Yes	No	Yes	Yes	Moderate
Sugawara et al. 1995 (rat)	Yes	No	No	Yes	Low
Suttle and Mills 1966 (pig, Experiment 1)	Yes	No	No	Yes	Low
Suttle and Mills 1966 (pig, Experiment 2)	Yes	No	No	Yes	Low
Temiz et al. 2021 (rat)	Yes	No	Yes	Yes	Moderate
Wu et al. 2020 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Copper–Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent Control Group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Yu et al. 2021a (rat)	Yes	Yes	Yes	Yes	High
Zhang et al. 2020 (pig)	Yes	No	Yes	Yes	Moderate
Oral chronic exposure					
Araya et al. 2012 (monkey)	Yes	No	Yes	Yes	Moderate
Outcome: Respiratory effects					
Inhalation acute exposure					
Poland et al. 2022 (rat, sulfate)	Yes	No	Yes	Yes	Moderate
Poland et al. 2022 (rat, oxide)	Yes	No	Yes	Yes	Moderate
Inhalation intermediate exposure					
Poland et al. 2022 (rat, oxide)	Yes	Yes	Yes	Yes	High
Johansson et al. 1983 (rabbit)	Yes	No	Yes	No	Low
Johansson et al. 1984 (rabbit)	Yes	No	Yes	No	Low
Oral intermediate exposure					
Chung et al. 2009 (rat)	Yes	Yes	Yes	Yes	High
Draper et al. 2023 (rat)	Yes	No	Yes	No	Low
NTP 1993 (mouse, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (mouse, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 15 days, water)	Yes	No	Yes	Yes	Moderate
NTP 1993 (rat, 15 days, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (mouse, 13 weeks, feed)	Yes	Yes	Yes	Yes	High
NTP 1993 (rat, 13 weeks, feed)	Yes	Yes	Yes	Yes	High

Table C-17. Initial Confidence Rating for Copper Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Gastrointestinal effects		
Oral acute exposure		
Animal Studies		
Husain et al. 2021	Low	Moderate
Yamamoto et al. 2004 (shrew)	Moderate	
Human studies		
Araya et al. 2001	High	High
Araya et al. 2003a	High	
Araya et al. 2003c	High	
Gotteland et al. 2001	High	
Olivares et al. 2001	High	
Pizarro et al. 1999	High	
Pizarro et al. 2001	High	
Oral intermediate exposure		
Animal studies		
Chung et al. 2009	High	High
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 day, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat,13 weeks, feed)	High	
Human studies		
Araya et al. 2003b, 2004	High	High
Olivares et al. 1998	High	
Pratt et al. 1985	Very Low	
Buchanan et al. 1999	Moderate	
Pettersson et al. 2003	Moderate	
Buchanan et al. 1999	Moderate	
Outcome: Hepatic Effects		
Inhalation acute exposure		
Animal studies		
Poland et al. 2022 (rat, sulfate)	Very Low	Very Low
Poland et al. 2022 (rat, oxide)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Poland et al. 2022 (rat, oxide)	Moderate	Moderate
Oral acute exposure		
Animal studies		
Alhusaini et al. 2018a (rat)	Moderate	Moderate

Table C-17. Initial Confidence Rating for Copper Health Effects Studies

	Initial study confidence	Initial confidence rating
Alhusaini et al. 2018b (rat)	Moderate	
Haywood 1980 (rat)	Low	
Haywood and Comerford 1980 (rat)	Low	
Human studies		
Pizarro et al. 1999	Moderate	Moderate
Pizarro et al. 2001	Moderate	
Oral intermediate exposure		
Animal studies		
Abe et al. 2008 (rat)	Moderate	High
Adele et al. 2023 (rat)	Low	
Chung et al. 2009 (rat)	Moderate	
Dab et al. 2023 (mouse)	Low	
Epstein et al. 1982 (rat)	Moderate	
Fuentealba et al. 2000 (rat)	Low	
Haywood 1980 (rat)	Low	
Haywood and Comerford 1980 (rat)	Low	
Haywood and Loughran 1985 (rat)	Moderate	
Kumar et al. 2015, 2016a, 2016b (rat)	High	
Kumar and Sharma 1987 (rat)	Low	
Liu et al. 2020a, 2020b, 2021a, 2021b (mouse)	Low	
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 days, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat,13 weeks, feed)	High	
Patwa and Flora 2020 (rat)	Moderate	
Rana and Kumar 1980 (rat)	High	
Sakhaee et al. 2012 (rat)	High	
Sakhaee et al. 2014 (mouse)	Moderate	
Seven et al. 2018 (rat)	Moderate	
Sugawara et al. 1995 (rat)	Low	
Suttle and Mills 1966 (pig, Experiment 1)	Low	
Suttle and Mills 1966 (pig, Experiment 2)	Low	
Temiz et al. 2021 (rat)	Moderate	
Wu et al. 2020 (mouse)	High	
Yu et al. 2021a (rat)	High	
Zhang et al. 2020 (pig)	Moderate	

Table C-17. Initial Confidence Rating for Copper Health Effects Studies

	Initial study confidence	Initial confidence rating
Human studies		
Araya et al. 2003b, 2004	Moderate	Moderate
O'Connor et al. 2003	Moderate	
Olivares et al. 1998	Moderate	
Pratt et al. 1985	Very Low	
Rojas-Sobarzo et al. 2013	Moderate	
Oral chronic exposure		
Animal studies		
Araya et al. 2012 (monkey)	Moderate	Moderate
Outcome: Respiratory effects		
Inhalation acute exposure		
Animal studies		
Poland et al. 2022 (rat, sulfate)	Moderate	Moderate
Poland et al. 2022 (rat, oxide)	Moderate	
Inhalation intermediate exposure		
Animal studies		
Poland et al. 2022 (rat, oxide)	High	High
Johansson et al. 1983 (rabbit)	Low	
Johansson et al. 1984 (rabbit)	Low	
Inhalation intermediate exposure		
Human studies		
Boogaard et al. 2013	Moderate	Moderate
Gehring et al. 2015	Moderate	
Yu et al. 2021b	Moderate	
Fouad and Ramadan 2022	Moderate	
Saadiani et al. 2023	Moderate	
Mourad and El-Sherif 2022	Moderate	
Oral intermediate exposure		
Animal studies		
Chung et al. 2009 (rat)	High	High
Draper et al. 2023 (rat)	Low	
NTP 1993 (mouse, 15 days, water)	Moderate	
NTP 1993 (mouse, 15 days, feed)	High	
NTP 1993 (rat, 15 days, water)	Moderate	
NTP 1993 (rat, 15 days, feed)	High	
NTP 1993 (mouse, 13 weeks, feed)	High	
NTP 1993 (rat, 13 weeks, feed)	High	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for gastrointestinal and hepatic effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with copper exposure is presented in Table C-19.

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Gastrointestinal effects			
Human studies	High	+1 Consistency in the body of evidence	High
Animal studies	High	+1 Consistency in the body of evidence	High
Outcome: Hepatic effects			
Human studies	Moderate	-1 Indirectness: length of time between exposure and outcome assessment	Low
Animal studies	High	+1 Consistency in the body of evidence	High
Outcome: Respiratory effects			
Human studies	Moderate	-1 Risk of bias	Low
Animal studies	High	None	High

Table C-19. Confidence in the Body of Evidence for Copper

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Gastrointestinal effects	High	High
Hepatic effects	Low	High
Respiratory effects	Low	High

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9, and C-10). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for copper, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome

- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for copper is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Copper

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human Studies			
Gastrointestinal effects	High	Health effect	High
Hepatic effects	Low	No health effect	Inadequate
Respiratory effects	Low	Health effect	Low
Animal Studies			
Gastrointestinal effects	High	Health effect	High
Hepatic effects	High	Health effect	High
Respiratory effects	High	Health effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

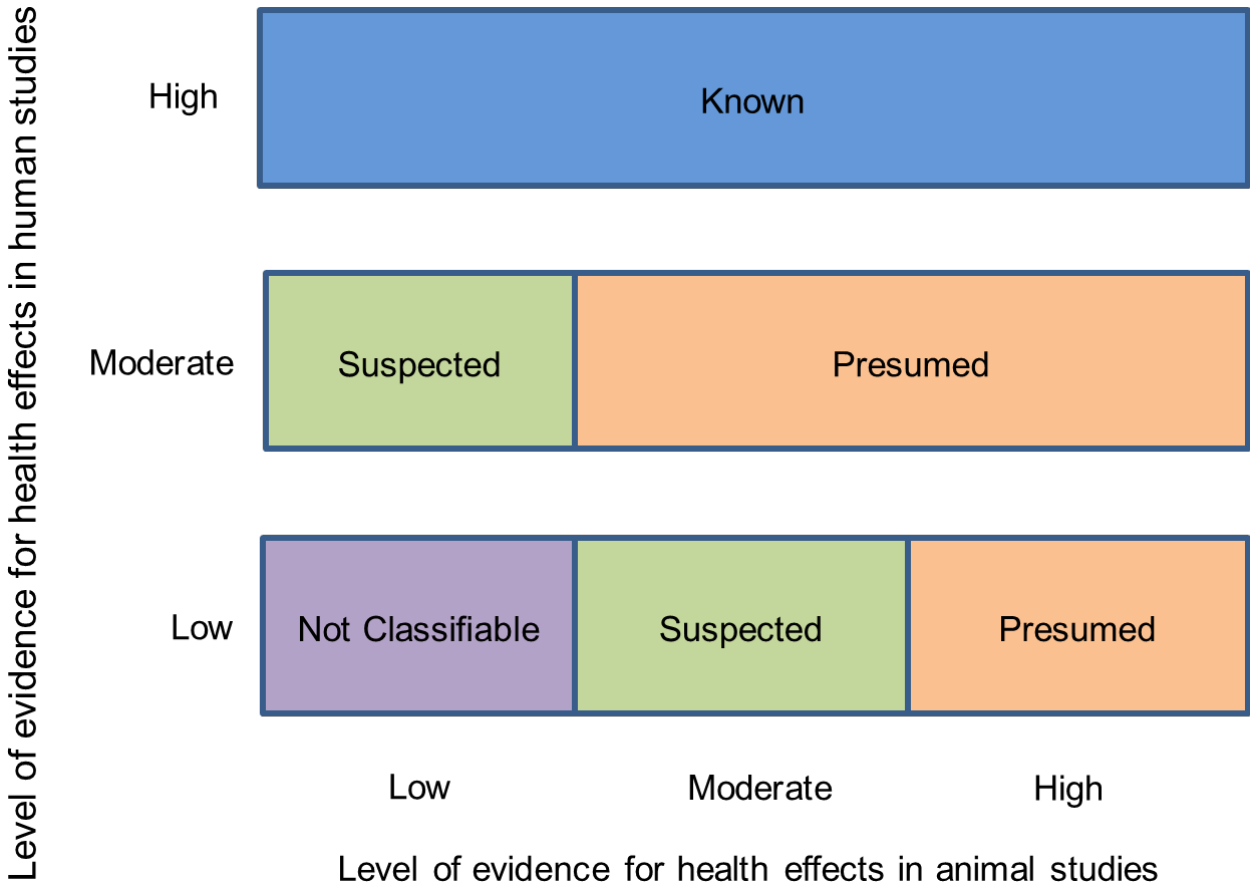
The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**

- Low level of evidence in human studies **AND** moderate level of evidence in animal studies

- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for copper are listed below and summarized in Table C-21.

Known Health Effects

- High level of evidence for gastrointestinal effects in humans exposed orally in controlled-exposure studies of acute-duration exposure to copper sulfate in drinking water (Araya et al. 2001, 2003a; Pizarro et al. 1999, 2001) and intermediate-duration exposure to copper sulfate in drinking water or other juice (Araya et al. 2003b, 2003c, 2004; Olivares et al. 2001). Supporting information comes from case reports/series (Banerjee et al. 2023; Bupta et al. 2023; Du and Mou 2019; Franchitto et al. 2008; Galust et al. 2023; Gamakaranage et al. 2011; Griswold et al. 2017; Hassan et al. 2010; Higny et al. 2014; Lubica et al. 2017; Malik and Mansur 2011; Shankar et al. 2023; Tsao et al. 2020) and community health investigations (Knobeloch et al. 1994, 1998).
- High level of evidence for gastrointestinal effects in mice, rats, and shrews from acute-duration exposure to copper chloride or copper sulfate (Husain et al. 2021; Yamamoto et al. 2004); and intermediate-duration exposure to copper monochloride or copper sulfate pentahydrate (Chung et al. 2009; NTP 1993).

Presumed Health Effects

Respiratory

- Low level of evidence for respiratory effects in humans exposed via inhalation based on epidemiological studies (Boogaard et al. 2013; Fouad and Ramadan 2022; Gehring et al. 2015; Mourad and El-Sherif 2022; Saadiani et al. 2023; Yu et al. 2021b). Supporting information comes from occupational health investigations (Askergren and Mellgren 1975; Plamenac et al. 1985; Suciu et al. 1981) and case reports of inhalation exposure (Donoso et al. 2007; Pimentel and Marques 1969; Pimentel and Menezes 1975; Stark 1981; Villar 1974; Villar and Nogueira 1980).
- High level of evidence for respiratory effects in rats exposed by inhalation for acute durations to copper sulfate pentahydrate or dicopper oxide (Poland et al. 2022) and for an intermediate duration to dicopper oxide (Poland et al. 2022). Respiratory effects were also seen in rats exposed orally to copper sulfate pentahydrate for an intermediate duration (Draper et al. 2023).

Hepatic

- Low level of evidence for hepatic effects in human studies; no changes in hepatic enzyme levels were observed after acute-duration (Pizarro et al. 1999, 2001) or intermediate-duration oral exposure to copper sulfate (Araya et al. 2003b, 2004; O'Connor et al. 2003; Olivares et al. 1998; Rojas-Sobarzo et al. 2013) or copper gluconate (Pratt et al. 1985). Information from occupational health investigations (Suciu et al. 1981), case reports (Du and Mou 2019; Griswold et al. 2017; Gunay et al. 2006; Hassan et al. 2010; Malik and Mansur 2011; Mortazavi and Jafari-Javid 2009; Shankar et al. 2023; Sinkovic et al. 2008; Yadla et al. 2015; Yang et al. 2004), and human mutations that result in copper accumulation suggest that hepatic effects are possible.
- High level evidence of effects in rats and mice exposed to copper compounds via oral administration for acute (Alhusaini et al. 2018a, 2018b; Haywood 1980; Haywood and Comerford 1980) and intermediate durations (Dab et al. 2023; Epstein et al. 1982; Fuentealba et al. 2000; Haywood 1980; Haywood and Comerford 1980; Haywood and Loughran 1985; Kumar et al. 2015, 2016a, 2016b; Kumar and Sharma 1987; Liu et al. 2020a, 2020b, 2021a, 2021b; NTP 1993; Patwa and Flora 2020; Rana and Kumar 1980; Sakhaee et al. 2012, 2014; Seven et al. 2018; Sugawara et al. 1995; Temiz et al. 2021; Wu et al. 2020; Yu et al. 2021a) and in pigs after intermediate-duration oral exposure (Suttle and Mills 1966).

Table C-21. Hazard Identification Conclusions for Copper

Outcome	Hazard identification
Gastrointestinal effects	Known
Hepatic effects	Presumed
Respiratory effects	Presumed

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints 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?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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 endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

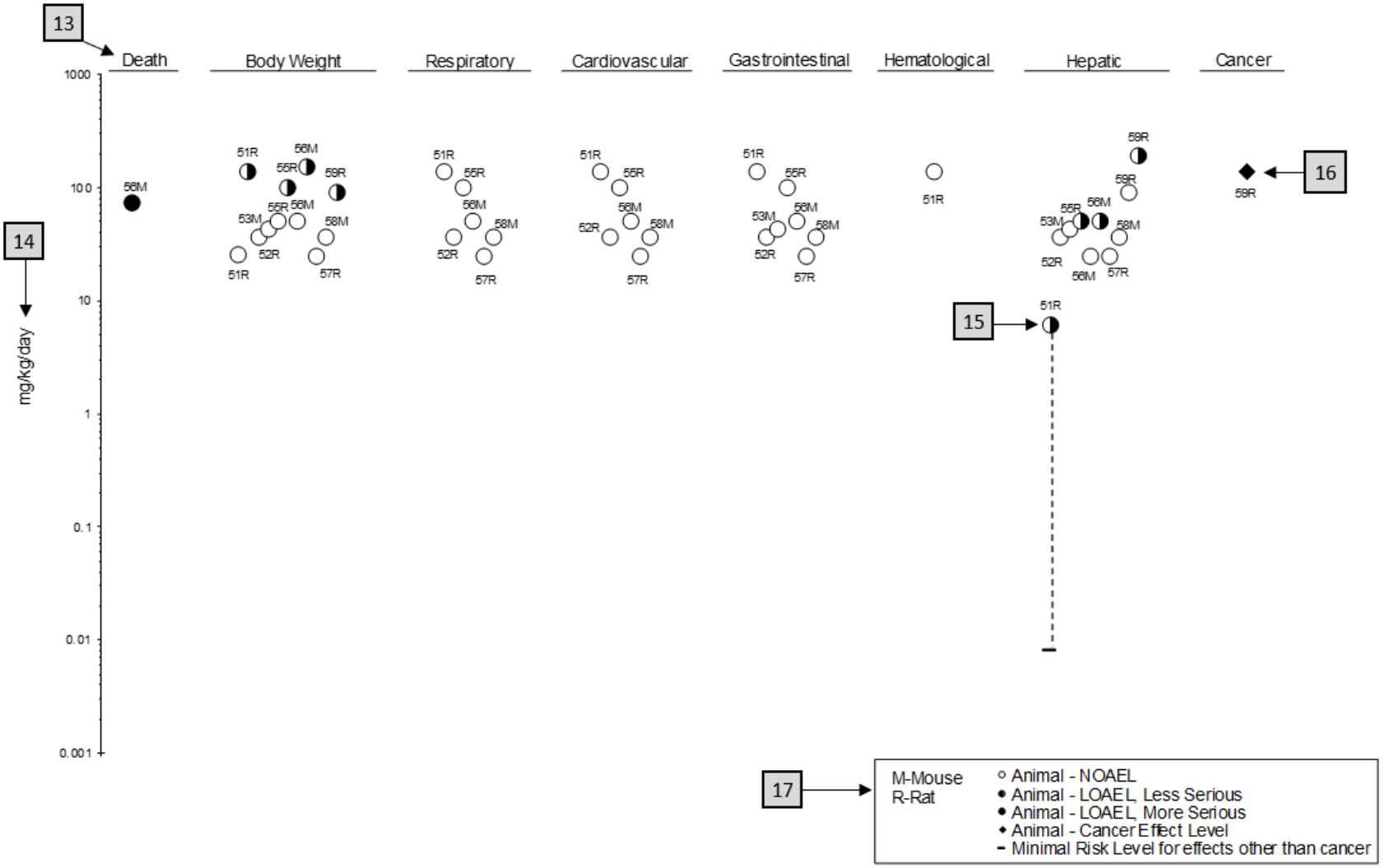
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. 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 may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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

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

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to 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, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

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, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—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.

Excretion—The process by which metabolic waste products are removed from the body.

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.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and 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.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

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

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

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the 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, which are changes 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 hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level 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. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is 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, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air 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 a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound 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 hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
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

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result