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

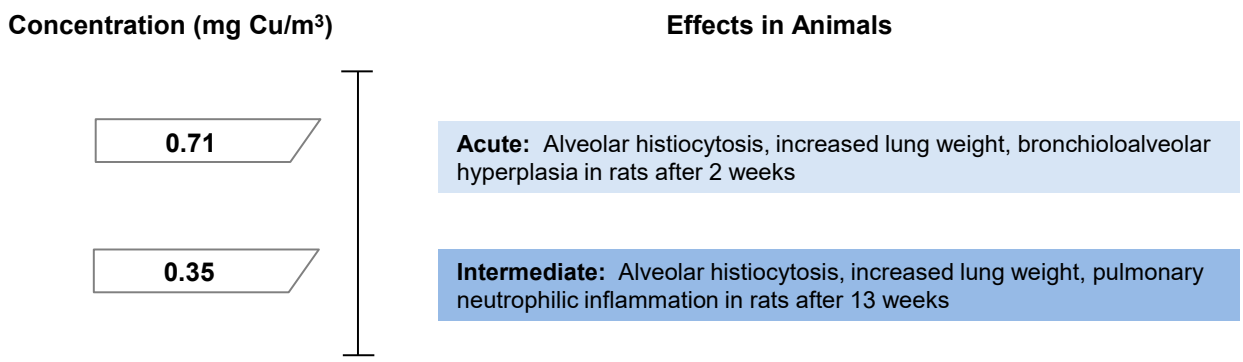
Information on the toxicity of copper and copper compounds comes primarily from oral studies in both humans and animals exposed to copper sulfate. The vast majority of human studies are case reports of accidental or intentional ingestion of copper compounds; however, several human controlled oral exposure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

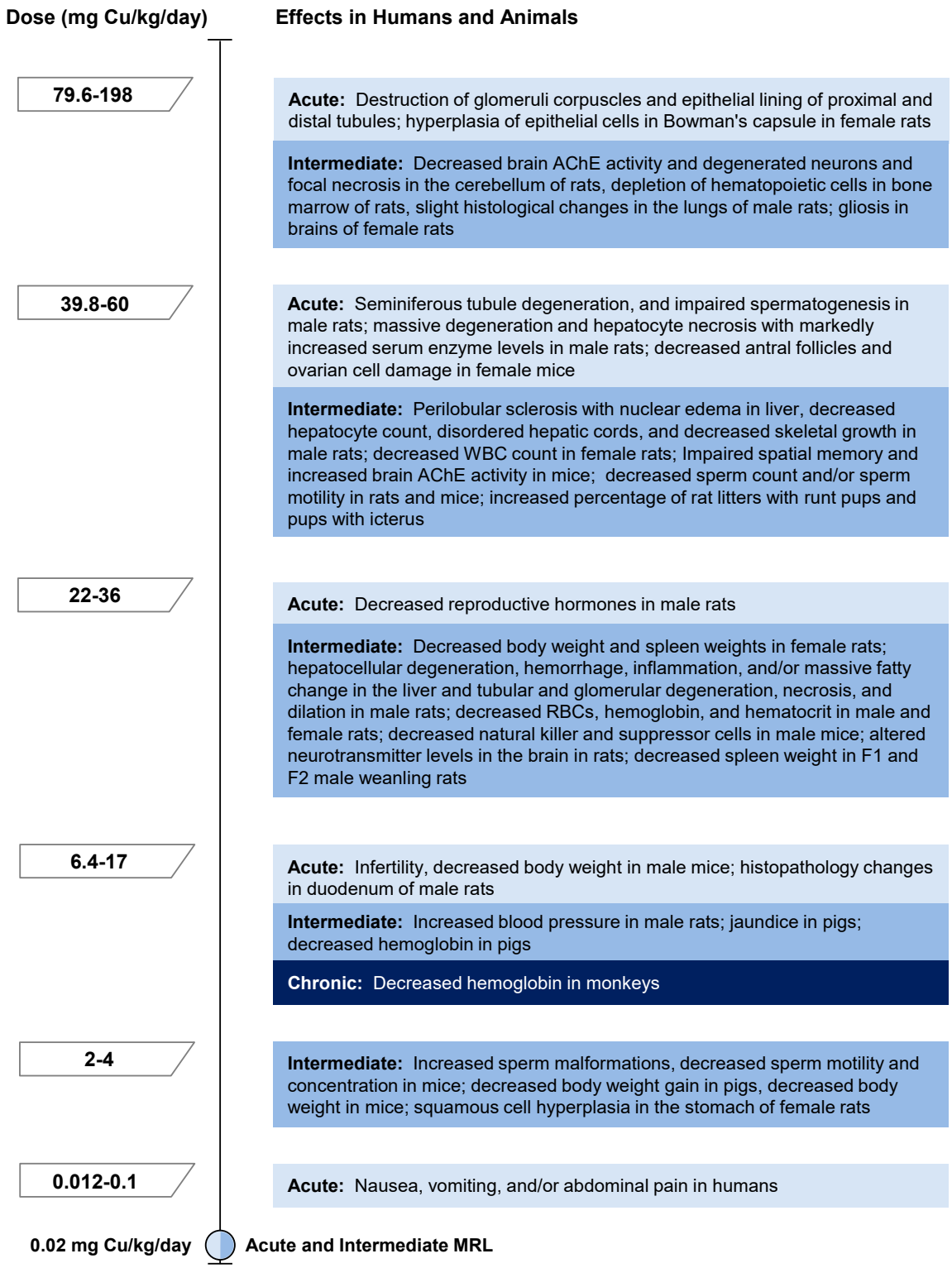
- Gastrointestinal effects are a known health effect for humans following oral exposure.
- Respiratory effects are a presumed health effect for humans following inhalation exposure.
- Hepatic effects are a presumed health effect for humans following oral exposure.

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.

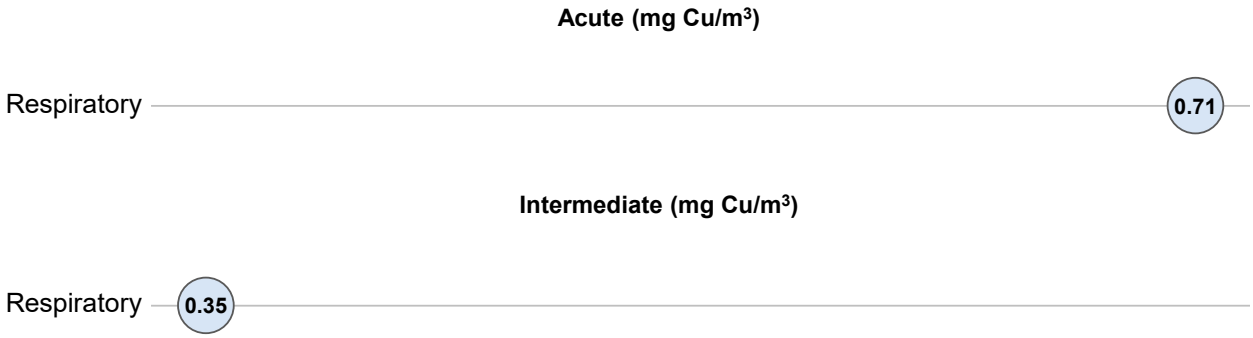


Figure 1-4. Summary of Sensitive Targets of Copper – Oral

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.

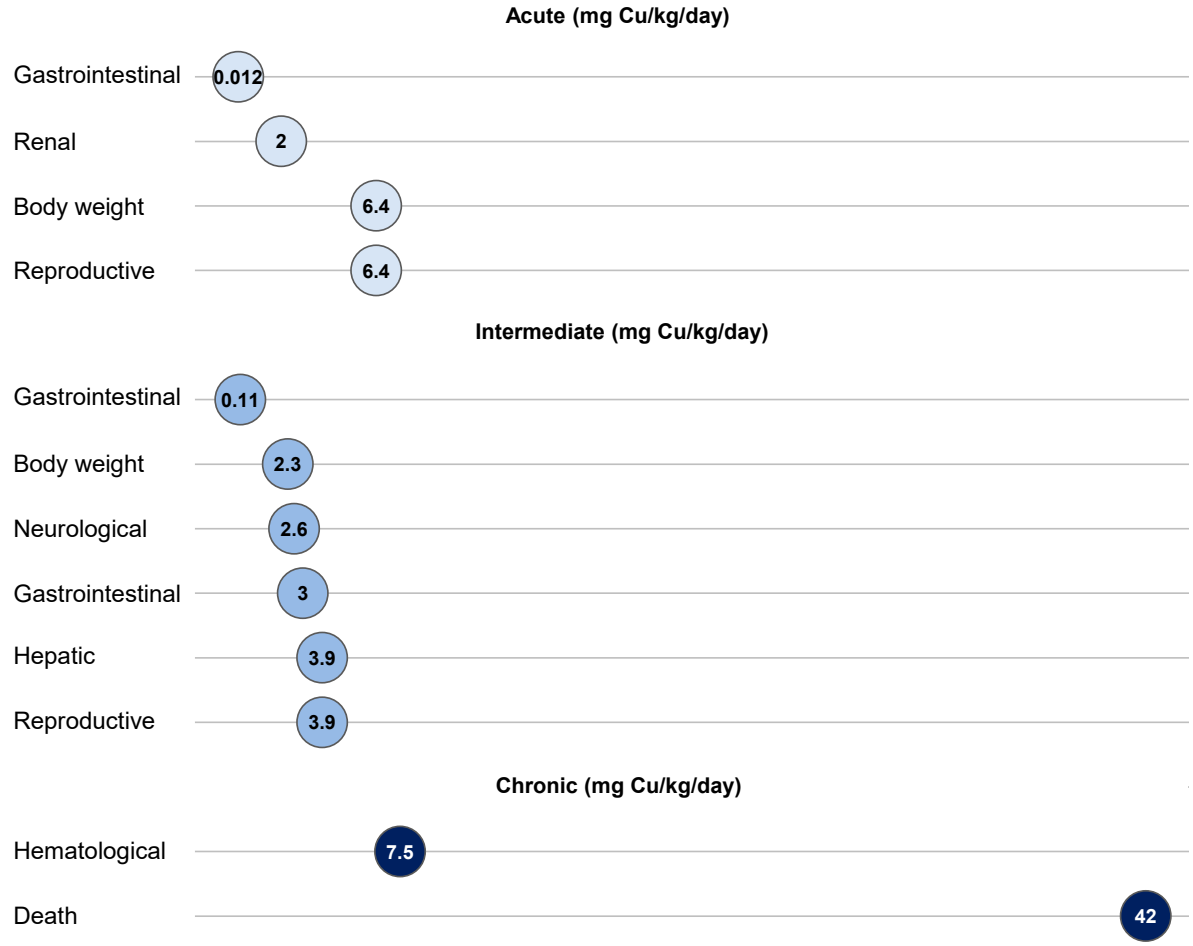


Table 1-1. Minimal Risk Levels (MRLs) for Copper[a]

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