

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Copper (Cu) is a chemical element and essential trace mineral that is a reddish metal which occurs naturally in rock, soil, sediment, water, and at low levels, air. The Earth's crust is the primary natural source of copper with an average copper concentration of 50 ppm (Henckens and Worrell 2020). Copper also occurs naturally in all plants and animals, and hence is found in foods and food supplements. The National Academies Institute of Medicine's Recommended Dietary Allowance (RDA) and Tolerable Upper Intake Level (UL) of copper for adult men and women is 900 µg/day and 10,000 µg/day, respectively, but these values vary for children and lactating and pregnant females. In the United States, the geometric mean serum copper level for all adults in the 2015-2016 NHANES was 1146.6 µg/L (18.1 µmol/L). Copper is an essential micronutrient necessary to humans and animals as it is required for adequate growth, lung elasticity, vascular function, neovascularization, neuroendocrine function, and iron metabolism (NRC 2000). However, excess intake of copper can result in toxicity and may adversely interact with certain heavy metals such as zinc. Copper is essential for body system functions, however, there is uncertainty as to the level at which copper becomes toxic. Excess copper exposure can result from external environmental sources such as copper contamination in drinking water, and endogenously from disorders that disturb copper regulation in the body. Copper contaminated water may have a light blue or blue-green color with a metallic, bitter taste (WHO 2004).

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 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, coating, textiles, and pharmaceuticals. The toxicity of copper nanoparticles is distinct from the toxicity of ionic

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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 as its salt but can also be exposed to other forms via inhalation and, to a lesser extent, dermally. In ambient air, the mean copper concentration across 15 U.S. sites ranged from 0.013 to 0.0792 $\mu\text{g}/\text{m}^3$ (EPA 2020a). Concentrations in drinking water can vary widely from ≤ 0.005 to 10.2 $\mu\text{g}/\text{L}$ (see Section 5.5.2). The EPA's action level for dissolved copper in drinking water is 1.3 $\mu\text{g}/\text{L}$. Soluble copper has been reported at various levels in a wide range of food products including fruits, meats, breads, processed foods, dairy, bottled water, and juices, among others. Copper is also measured in blood, urine, hair and 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 or copper sulfate, the most commonly used compound. Human studies include controlled-exposure and epidemiological studies, and primarily examine the effect of different copper doses from diet and drinking water. Additionally, human studies have also examined the associations of copper in biological fluids or copper in the environment with various health outcomes. Oral toxicity studies evaluate various deficiency or toxicity endpoints, and the gastrointestinal and hepatic systems are the most studied endpoints and appear to be sensitive endpoints of copper exposure. These two endpoints underwent systematic review. There were fewer studies examining inhalation or dermal exposure to copper in humans and animals. A limited number of studies in both humans and animals examined copper toxicity due to inhalation or dermal exposure. The genotoxicity of copper and copper compounds has been evaluated using a variety of species and protocols. Disorders such as Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis are characterized by excess copper build-up in the body, primarily the liver, and typically result in liver damage. These disorders are further described in Section 2.9. Figure 1-1 and Figure 1-2 summarize the health effects observed in human and animal inhalation and oral studies, respectively. Taken together, the database demonstrates that the most sensitive endpoints for copper toxicity appear to be the gastrointestinal and hepatic systems. A systematic review was conducted on these endpoints. The weight-of-evidence conclusions are defined and summarized in Appendix C.

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The review resulted in the following hazard identification¹ conclusions:

- Gastrointestinal effects are presumed health effects from exposure to copper.
- Hepatic effects are suspected health effects from exposure to copper.

Gastrointestinal Effects. Numerous case studies and epidemiological studies have reported gastrointestinal upset in humans from oral exposure to copper supporting the finding that the gastrointestinal system is a target of copper toxicity. Copper is absorbed rapidly by the stomach and intestine when ingested, and induces abdominal pain, nausea, and vomiting as reported in communities episodically exposed to excess levels of copper in their drinking water (Eife et al. 1999; Knobloch et al. 1994, 1998; Pizarro et al. 2007) and in some occupational settings (Suciu et al. 1981). 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). In adults, the incidence of gastrointestinal symptoms (i.e., nausea, vomiting, abdominal pain) was higher in subjects repeatedly exposed to copper doses ranging from 0.07 to 0.17 mg Cu/kg/day (3 to 6 mg Cu/L) (Araya et al. 2003b, 2004; Pizarro et al. 1999, 2001). However, diarrhea does not appear to be associated with exposure at these low copper concentrations (Pizarro et al. 1999, 2001). Females appear to be more sensitive to copper, developing gastrointestinal symptoms at lower doses compared to males (Araya et al. 2004). A study with infants observed no increase in the gastrointestinal symptoms following daily exposure to doses up to 0.319 mg Cu/kg/day (2 mg Cu/L) in drinking water for 9 months (Olivares et al. 1998). Several studies where adults were exposed to single doses of copper ranging from 0.012 to 0.18 mg Cu/kg (4 to 12 mg Cu/L) in drinking water found that nausea is the most reported gastrointestinal symptom (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001). Vomiting was also reported following exposure to single doses of 0.018 to 0.037 mg Cu/kg (6 to 12 mg Cu/L) (Gotteland et al. 2001; Olivares et al. 2001). Other gastrointestinal effects induced by copper included delayed gastric emptying (Araya et al. 2003a) and increased gastric permeability (Gotteland et al. 2000), both of which were independent of the gastrointestinal symptoms. Evidence in laboratory animals indicates that oral copper exposure results in histological changes, such as ulcerations throughout the gastrointestinal tract, and changes in intestinal microbiome homeostasis at doses ≥ 2.4 mg Cu/kg/day (Cheng et al. 2020; Kadammattil et al. 2018;

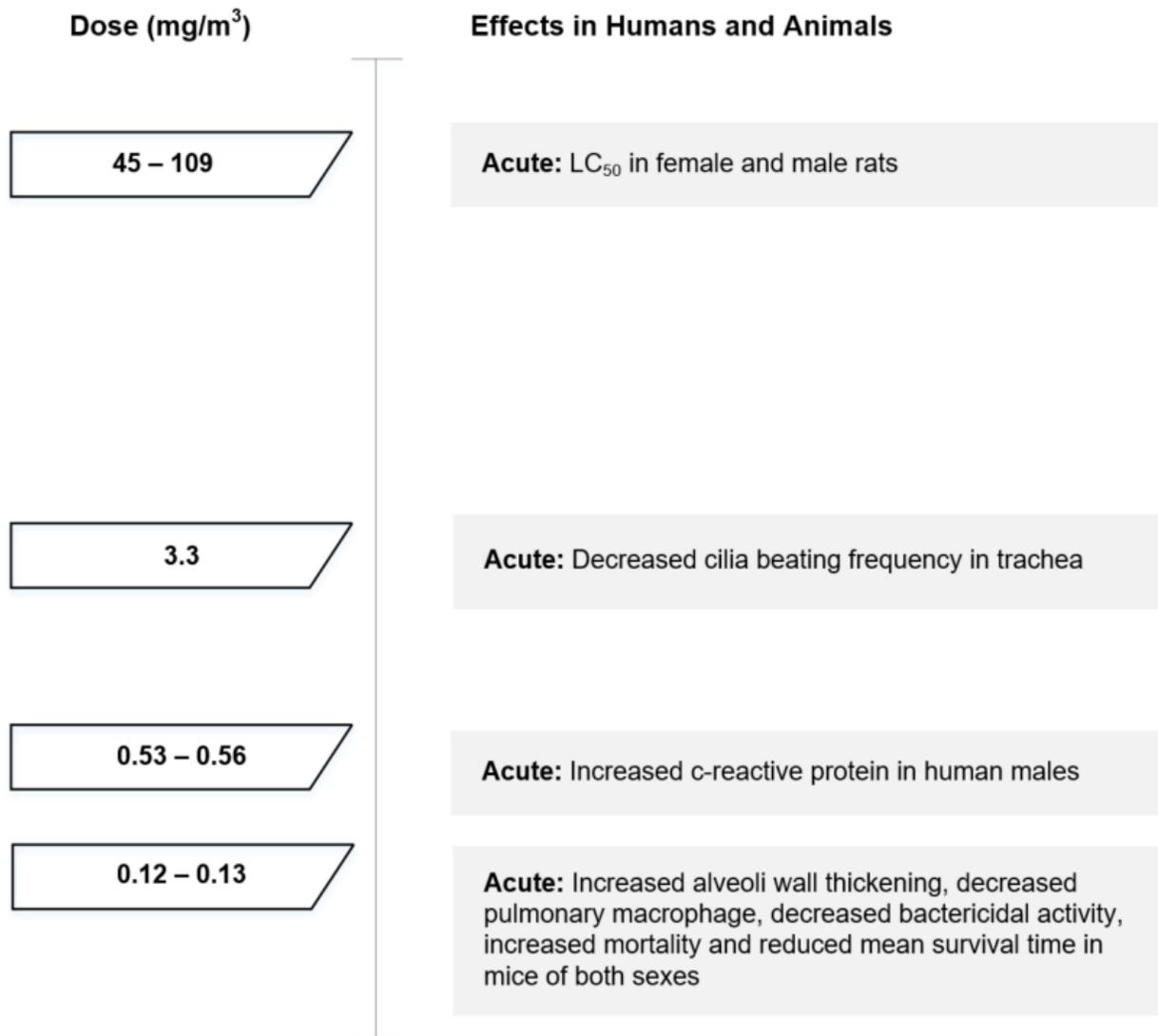
¹ For additional details on the definitions on the hazard identification categories the reader is referred to Appendix C.

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Khushboo et al. 2018; NTP 1993; Yamamoto et al. 2004). Pregnant rabbits exposed to high copper doses had diarrhea, stomach hemorrhage, ulcerations, and discolored stomach lining (Munley 2003a, 2003b).

Hepatic Effects. Human case studies report increases in liver enzymes (i.e., alanine aminotransferase, aspartate aminotransferase), 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; Park et al. 2018; Pratt et al. 1985). Controlled-exposure studies, where humans were exposed to lower levels of copper in drinking water, found no alterations or indications of damage to the liver, including studies in infants (Olivares et al. 1998; Zietz et al. 2003a, 2003b) and adults (O'Connor et al. 2003). Individuals with Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis are particularly susceptible to liver toxicity caused by altered copper homeostasis. These diseases can be exacerbated by excess oral copper intake (i.e. consuming milk boiled or stored in brass vessels) relative to the ability of the liver to safely store copper. Evidence of hepatotoxicity resulting from excess copper exposure primarily comes from laboratory animal experiments, and most of these studies examined rats. Liver effects were seen in doses as low as 1.6 mg Cu/kg/day in experimental animals exposed daily for 30 days, effects included elevated hepatic marker enzymes, lipid damage, and extensive histopathological observations in the liver such as acute swelling of hepatocytes, coagulative necrosis represented by karyolysis of nuclei, and hyperplasia of the epithelial lining of bile ducts (Hashish and Elgaml 2016). Similar or more severe hepatic changes were noted in acute- and intermediate-duration exposure studies. Additional effects include reduced liver weight, massive cellular degeneration, liver hemorrhage from acute-duration exposure (Alhusaini et al. 2018a, 2018b; Kadammatil et al. 2018); and centrilobular necrosis, enlarged liver, jaundice and hepatic lesions from intermediate-duration exposure (Khushboo et al. 2018; Rana and Kumar 1980; Sakhae et al. 2012; Seven et al. 2018; Suttle and Mills 1966). NTP (1993) noted the effects in the liver were dose-related, and Kumar et al. (2016a) reported that increased severity of histological findings in rats were dose- and duration-related.

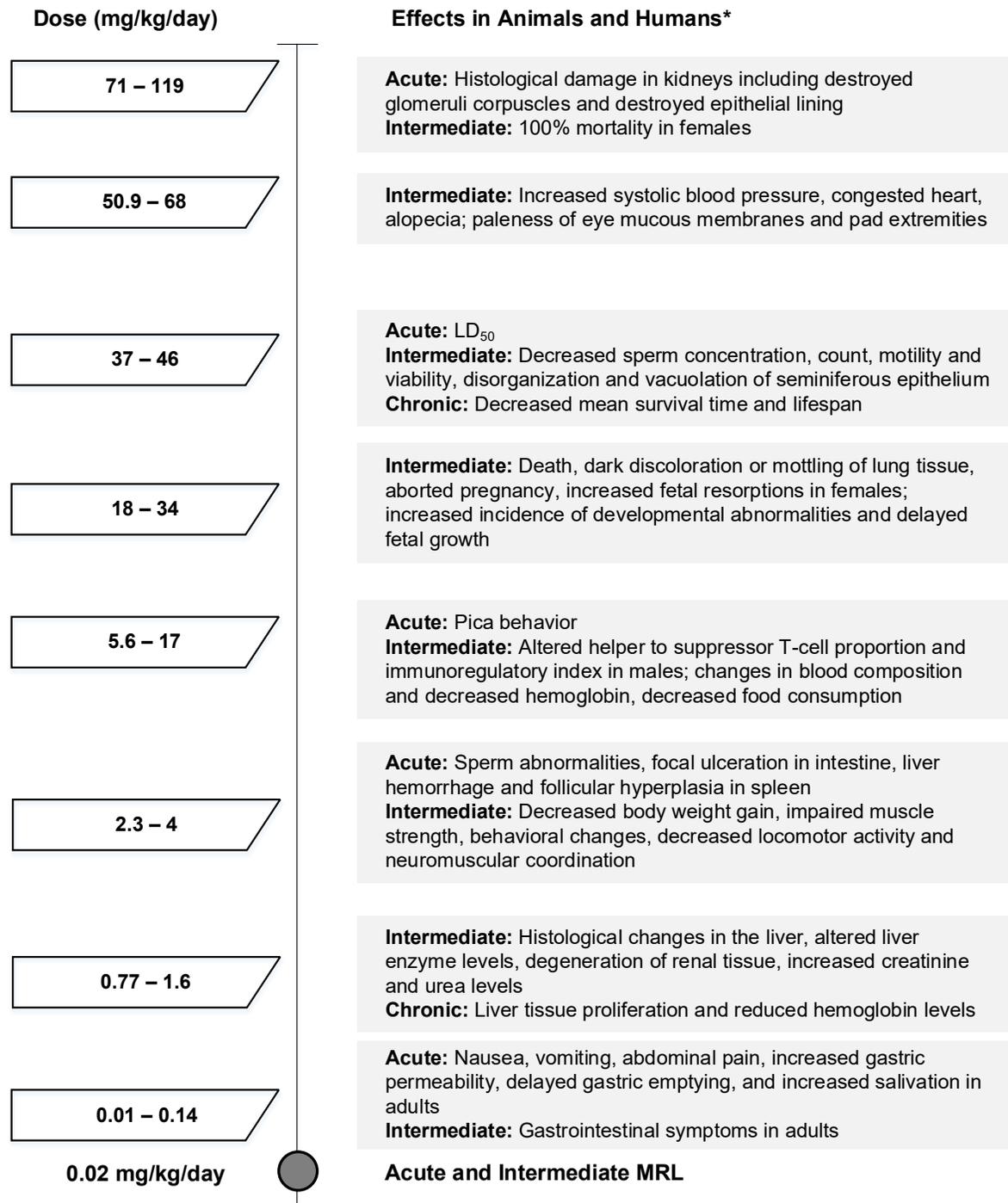
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Figure 1-1. Health Effects Found in Humans and Animals* Following Inhalation Exposure to Copper

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

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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.

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1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3 following acute-duration inhalation exposure, the respiratory and immunological systems are the most sensitive targets of copper toxicity. The inhalation database was inadequate for the derivation of inhalation minimal risk levels (MRLs) for any duration of exposure. The gastrointestinal, hepatic, and neurological systems appear to be sensitive targets of oral copper toxicity, as shown in Figure 1-4. The oral database was adequate for the derivation of acute-duration oral MRL for copper. The acute-duration oral MRL was also used as the intermediate-duration oral MRL. There was insufficient data for the derivation of an oral chronic MRL for copper. MRLs derived for the oral exposure route for copper are summarized in Table 1-1 and are discussed in greater detail in Appendix A.

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

The respiratory and immunological systems are the most sensitive targets of copper inhalation exposure.

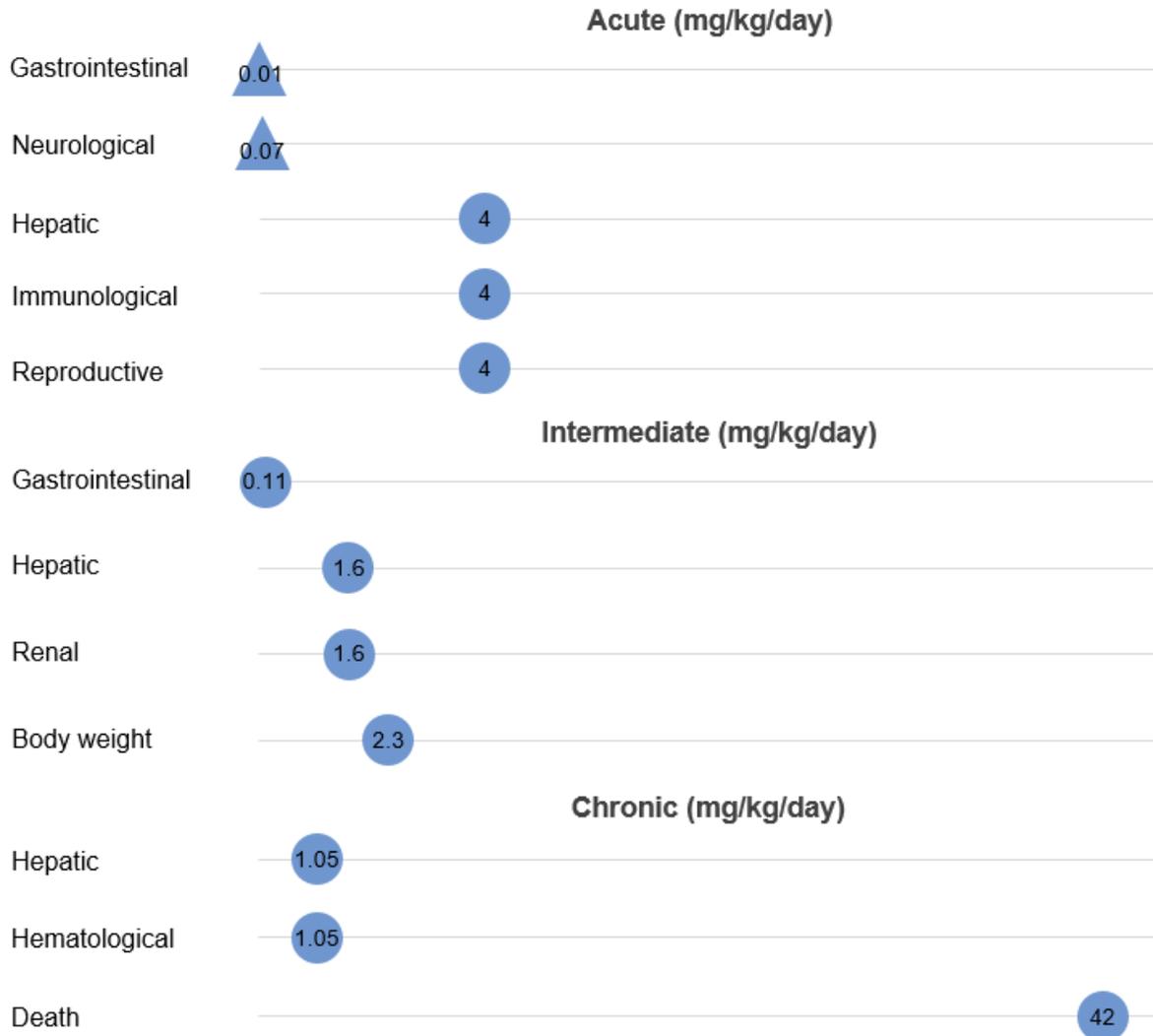
Numbers in circles are the lowest LOAELs among health effects in animals.



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

The gastrointestinal, hepatic, 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.



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

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty & modifying factor	Reference
Inhalation exposure (mg Copper/m³)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg Copper/kg/day)					
Acute (provisional)	0.02	Gastrointestinal symptoms in women	BMDL ₁₀ : 0.05	UF: 3	Pizarro et al. 1999
Intermediate (provisional)	The provisional acute-duration oral MRL of 0.02 mg/kg/day is adopted as the provisional intermediate-duration oral MRL.				
Chronic	Insufficient data for derivation of an MRL				

^aSee Appendix A for additional information

BMDL = 95% lower confidence limit on the BMD (subscript denotes benchmark response of exposure dose associated with 10% extra risk); LOAEL = lowest-observed-adverse-effect-level; UF = uncertainty factor