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.

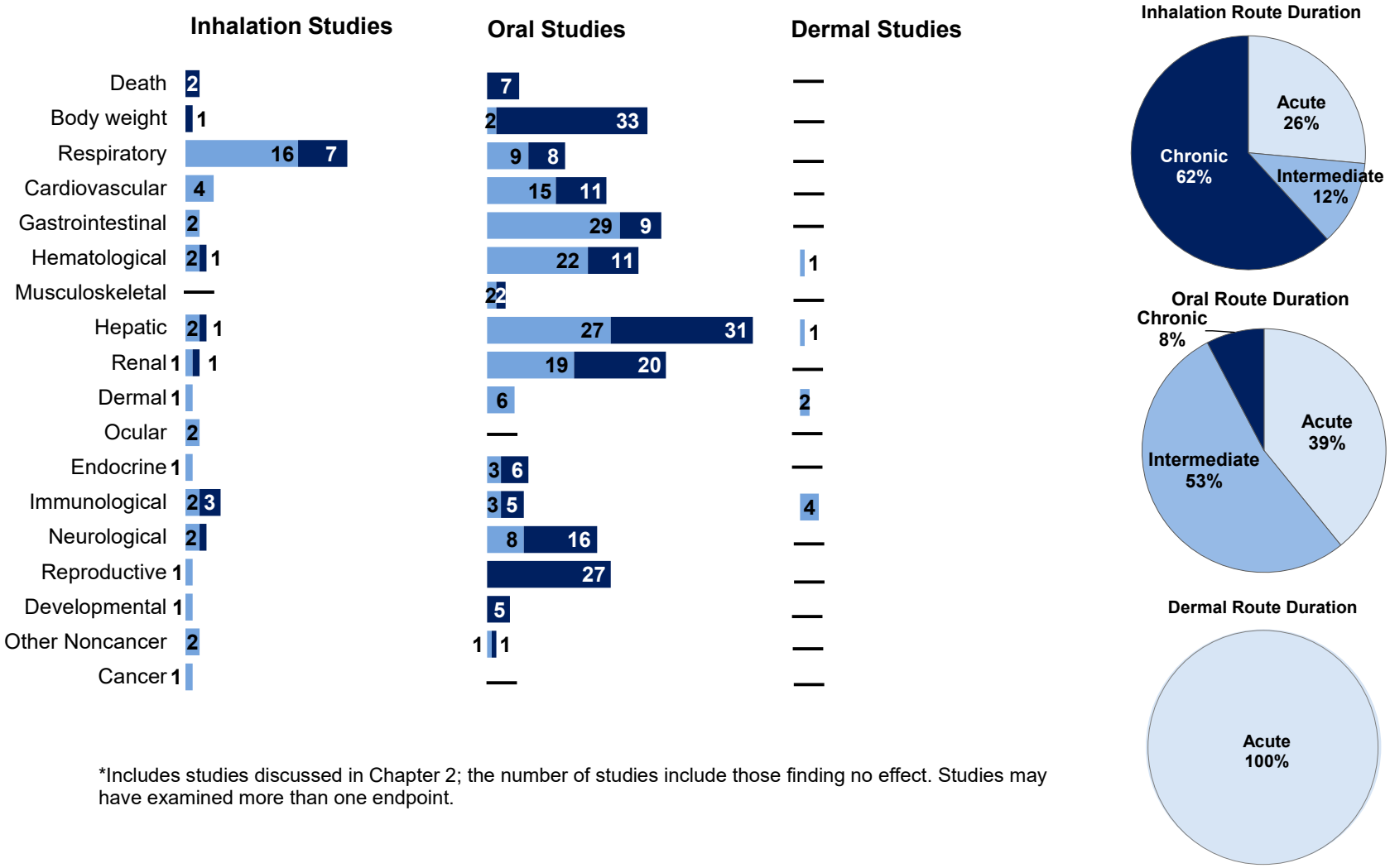
6.1 INFORMATION ON HEALTH EFFECTS

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)