2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COPPER IN THE UNITED STATES

Copper is a metallic element that occurs naturally as the free metal, or associated with other elements in compounds that comprise various minerals. Most copper compounds occur in +1 Cu(I) and +2 Cu(II) valence states. Copper is primarily used as a metal or an alloy (e.g., brass, bronze, gun metal). Copper sulfate is used as a fungicide, algicide, and nutritional supplement. Copper particulates are released into the atmosphere by windblown dust; volcanic eruptions; and anthropogenic sources, primarily copper smelters and ore processing facilities. Copper particles in the atmosphere will settle out or be removed by precipitation, but can be resuspended into the atmosphere in the form of dust. The mean concentration of copper in ambient air in the United States ranges from 5 to 200 ng/m^3. Copper is released into waterways by natural weathering of soil and rocks, disturbances of soil, or anthropogenic sources (e.g., effluent from sewage treatment plants). Copper concentrations in drinking water vary widely as a result of variations in pH and hardness of the water supply; the levels range from a few ppbs to 10 ppm. The mean concentration of copper in soil in the United States ranges from 5 to 70 mg/kg. The estimated daily intake of copper from food is 1.0–1.3 mg/day for adults (0.014–0.019 mg/kg/day).

The general population is exposed to copper through inhalation, consumption of food and water, and dermal contact with air, water, and soil that contains copper. The primary source of copper intake is the diet; however, the amount of copper in the diet usually does not exceed the average dietary requirements (RDAs) for copper. Drinking water is the primary source of excess copper. Populations living near sources of copper emissions, such as copper smelters and refineries and workers in these and other industries may also be exposed to high levels of copper in dust by inhalation. Copper concentrations in soils near copper emission sources could be sufficiently high to result in significantly high intakes of copper in young children who ingest soil. For example, copper concentrations of 2,480–6,912 ppm have been measured near copper smelters. These levels of copper in soils would result in the intake of 0.74–2.1 mg copper per day in a child ingesting 300 mg of soil. Copper has been identified in at least 906 of the 1,647 hazardous waste sites that have been proposed for inclusion on the EPA NPL.

2.2 SUMMARY OF HEALTH EFFECTS

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

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

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

The liver is also a sensitive target of toxicity. Liver damage (necrosis, fibrosis, abnormal biomarkers of liver damage) have been reported in individuals ingesting lethal doses of copper sulfate. Liver effects have also been observed in individuals diagnosed with Wilson’s disease, Indian childhood cirrhosis, or idiopathic copper toxicosis (which includes Tyrollean infantile cirrhosis). These syndromes are genetic disorders that result in an accumulation of copper in the liver; the latter two syndromes are associated with excessive copper exposure. Inflammation, necrosis, and altered serum markers of liver damage have been observed in rats fed diets with copper sulfate levels that are at least 100 times higher than the nutritional requirement. Damage to the proximal convoluted tubules of the kidney has also been observed in rats. The liver and kidney effects usually occur at similar dose levels; however, the latency period for the kidney effects is longer than for the liver effects.

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

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

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

Gastrointestinal Effects. The available human and animal data suggest that the gastrointestinal tract is a sensitive target of toxicity. There are numerous reports of nausea, vomiting, and/or abdominal pain in humans ingesting beverages contaminated with copper or water containing copper sulfate. These symptoms typically occur shortly after ingestion and are not persistent. The results of three single exposure studies suggest that the threshold for gastrointestinal symptoms is between 4 and 6 ppm, which is equivalent to doses of 0.11 mg/kg and 0.017–0.018 mg Cu/kg. Nausea, vomiting, and/or abdominal pain also appear to be the most sensitive end point following repeated exposure to copper in drinking water. These symptoms were reported by adults drinking water containing ≥3 ppm copper as copper sulfate (0.0731 mg Cu/kg/day) for 1–2 weeks or 4 ppm copper as copper sulfate (0.091 mg Cu/kg/day) for 2 months. Similar gastrointestinal effects were observed in adults ingesting copper oxide in drinking water. Although gastrointestinal irritation may play a role in the observed gastrointestinal effects, data from ferrets and monkeys suggest that vagal afferent fibers and 5-HT$_3$ and 5-HT$_4$ receptors are involved in copper-induced emesis.

Hepatic Effects. In humans, copper-induced hepatic damage is dependent on several factors including genetics, age, and copper intake. Liver damage is rarely reported in adults; the few reported cases of liver damage (centrilobular necrosis, jaundice, and increased aspartate aminotransferase activity) have been associated with intentional ingestion of a lethal dose of copper sulfate. In infants and children, reported liver effects are usually manifested in one of three syndromes: Wilson’s disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. Wilson’s disease is an autosomal recessive genetic disorder associated with impaired copper metabolism. Dietary exposure to higher than normal levels of copper does not appear to be necessary for the manifestation of liver damage. Some heterozygous carriers of Wilson’s disease also have elevated hepatic levels of copper and increased urinary excretion, although adverse health effects have not been reported in these individuals. There is evidence that Indian childhood cirrhosis and idiopathic copper toxicosis are also caused by a genetic defect that is transmitted in an autosomal recessive mode. However, unlike Wilson’s disease, manifestation of the disease is associated with exposure to unusually high levels of dietary copper from milk stored in copper or brass containers or from drinking water. The clinical age of onset is usually between 6 months and 5 years, and the observed liver effects include pericellular fibrosis, abnormal biochemical markers of liver damage (e.g., increased serum aspartate aminotransferase and alkaline phosphatase activities and serum bilirubin levels), and very high levels of copper in the liver. In general, the potential hepatotoxicity of copper has not been extensively investigated in healthy humans. No effect levels of 0.14–0.17 and 0.315 mg Cu/kg/day for liver effects in adults and infants (3–12 months of age), respectively, had been reported in intermediate-duration studies (2–9 months); these studies used serum chemistry biomarkers (e.g., alanine aminotransferase, aspartate aminotransferase) to assess liver damage. Two community survey studies also found no evidence of liver damage in infants living in households with 0.8 ppm copper in drinking water. The results of the three studies involving infants should be interpreted cautiously due to the high drop out rate, small number of subjects examined for possible liver damage, and the dismissal of anomalous findings as secondary to infection rather than possibly indicative of copper toxicity.

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

2.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

Inhalation MRLs

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs. Data on the inhaled toxicity of copper in humans following acute-duration exposure are limited to a report of workers developing metal fume fever while cutting brass pipe with an electric cutting tool in a poorly ventilated area (Armstrong et al. 1983); exposure levels were not reported. Respiratory effects and impaired immune function have been observed in mice following a single 3-hour exposure to 3.3 mg Cu/m^3 as copper sulfate or repeated exposure (3 hours/day, 5 days/week for 1–2 weeks) to 0.12–0.13 mg Cu/m^3 as copper sulfate (Drummond et al. 1986). The Drummond et al. (1986) study was not selected as the basis of an acute-duration inhalation MRL because a small number of animals was tested (four per group) and a limited number of end points (respiratory tract and immune function) were examined. Intermediate-duration data are limited to studies by Johansson et al. (1983, 1984), which did not find any histological alterations in the lungs or functional or morphological alterations in alveolar macrophages of rabbits exposed to copper chloride. As with the acute-duration data, the limited number of end points examined precludes deriving an intermediate-duration inhalation MRL. The chronic-duration database for copper consists of two occupational exposure studies reporting respiratory (Askergren and Mellgren 1975; Suciu et al. 1981) and gastrointestinal (Suciu et al. 1981) irritation, hepatic effects (Suciu et al. 1981), and possible neurological and reproductive effects (Suciu et al. 1981). Chronic-duration inhalation MRLs cannot be derived from these studies due to poor exposure characterization and/or lack of controls.

Oral MRLs

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to copper.

The available human and animal acute-duration studies strongly suggest that the gastrointestinal tract is the most sensitive target of copper toxicity. Numerous studies and case reports have reported nausea, vomiting, and/or abdominal pain in humans immediately following ingestion of copper-contaminated water or other beverages (Araya et al. 2001, 2003a, 2003b, 2003c; Chuttani et al. 1965; Gotteland et al. 2001; Knobeloch et al. 1994; Nicholas and Brist 1968; Olivares et al. 2001; Pizarro et al. 1999, 2001; Spitalny et al. 1984). In human studies involving a single exposure to copper following an overnight fast, adverse gastrointestinal effects (nausea, vomiting, abdominal pain, and/or diarrhea) have been observed at doses of 0.011–0.03 mg Cu/kg (Araya et al. 2001, 2003a, 2003c; Gotteland et al. 2001; Olivares et al. 2001). Under these experimental conditions, the apparent threshold appears to fall between 0.011 and

0.017 mg Cu/kg (Araya et al. 2001, 2003a; Olivares et al. 2001). Slightly higher thresholds for gastrointestinal symptoms were observed in two acute-duration repeated exposure studies in which subjects used a copper-containing water as their primary source of drinking water for 1 or 2 weeks (Pizarro et al. 1999, 2001). In the 2-week study, 60 women were given copper sulfate containing water to be used for drinking and cooking purposes. No significant alterations in serum biomarkers of liver damage (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase) were observed in the subjects at the end of the study. An increased occurrence of nausea, vomiting, and/or abdominal pain was observed when the women were exposed to 3 ppm copper as copper sulfate (0.0731 mg Cu/kg/day) (Pizarro et al. 1999); no significant increases in the incidence of gastrointestinal symptoms were noted at 1 ppm (0.0272 mg Cu/kg/day). Nausea, vomiting, and/or abdominal pain were also reported by women ingesting water containing 5 ppm (0.096 mg Cu/kg/day) as copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). Animal studies support the identification of the gastrointestinal tract as a sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

The Pizarro et al. (1999) 2-week study was selected as the basis of the acute-duration oral MRL for copper. This study identified no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 0.0272 and 0.0731 mg Cu/kg/day for increases in the incidence of nausea, vomiting, and/or abdominal pain. Although the LOAEL values identified in the single exposure studies (Araya et al. 2001, 2003; Olivares et al. 2001) are slightly lower than the than the NOAEL identified in the Pizarro et al. (1999) study, the Pizarro et al. (1999) study was selected as the critical study because it is a longer-duration study and it more closely mimics an exposure scenario of a population drinking copper-contaminated drinking water. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an acute-duration oral MRL of 0.01 mg Cu/kg/day. The observed gastrointestinal effects were probably due to direct contact; thus, only a partial uncertainty factor of 3 was used to account for human variability because toxicokinetic differences among individuals should not affect sensitivity. The acute-duration MRL is intended to protect against the health effects associated with exposure to copper-contaminated drinking water; it assumes that the affected population will have a normal intake of copper from the diet.

- An MRL of 0.01 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to copper.

There are limited data on the intermediate-duration toxicity of copper in humans. Araya et al. (2003b) exposed groups of 327–355 adults to <0.01 (control group), 2, 4, or 6 ppm copper sulfate in water for 2 months. The subjects prepared the copper sulfate solution to be used at home by mixing a stock copper sulfate solution with tap water; this solution was used for drinking water and preparing beverages and soups. Exposure to copper sulfate resulted in increases in the occurrence of gastrointestinal symptoms; the incidence was significantly higher than controls at 6 ppm when the data were analyzed using the chi-square test with Bonferroni correction and at 4 ppm when the Bonferroni correction was not used. Only one test was used to assess whether exposure to copper results in adverse gastrointestinal effects (reported symptoms); thus, the Bonferroni correction is not needed for this end point. Therefore, the 4 ppm concentration is identified as the LOAEL and the 2 ppm concentration as the NOAEL. The study authors reported copper intakes for 48–49 subjects per group who provided blood samples; no information on selection criteria were provided. The copper intakes were 0, 0.042, 0.091, and 0.17 mg Cu/kg/day for the control, 2, 4, and 6 ppm groups, respectively. The dietary intake of copper was not measured in this study; however, Araya et al. (2003b) noted that copper intake found in a survey of other community residents was 0.9 mg Cu/day. No significant alterations in copper status or liver function (as assessed by serum alanine aminotransferase, asparatate aminotransferase, and γ-glutamyl transferase activities) were observed in a subset of subjects from each group. In a study by Pratt et al. (1985), a group of seven adults were administered 10 mg Cu/day (0.14 mg Cu/kg/day) as copper gluconate in a capsule for 12 weeks. No significant alterations in serum markers of liver damage (cholesterol and triglyceride levels and serum aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and lactate dehydrogenase activities) were found. Similarly, no alterations in total bilirubin or serum alanine aminotransferase, aspartate aminotransferase, or γ-glutamyl transferase activities were observed in infants exposed to 0.315 mg Cu/kg/day for 9 months (Olivares et al. 1998). Zietz et al. (2003a, 2003b) also did not find evidence of liver damage in infants living in households with water concentrations of 0.8 ppm and higher. The Pratt et al. (1985), Olivares et al. (1998), and Zietz et al. (2003a, 2003b) studies did not report significant alterations in the occurrence of gastrointestinal disturbances and the study design did not include symptoms questionnaires, although the high dropout rate observed in the Olivares et al. (1998) study may have been related to gastrointestinal effects. Severe liver damage (pericellular fibrosis and increased serum aminotransferase and alkaline phosphatase activities) has been observed in children with a genetic susceptibility to high levels of copper in the liver. The liver was a critical target of toxicity in rats exposed to very high levels of copper in diet (greater than 100 times the nutritional requirement), Inflammation, necrosis, and increased alanine and aspartate aminotransferases activities have been reported in rats at exposure levels of 16 mg Cu/kg/day as copper sulfate in the diet (Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a; NTP 1993). No liver effects where observed at 8 mg Cu/kg/day (NTP 1993). Histological alterations in stomach, indicative of irritation (hyperplasia of the squamous mucosa on the limiting ridge separating the forestomach from the glandular stomach), have also been observed in rats and mice exposed to 33 or 267 mg Cu/kg/day, respectively, as copper sulfate in the diet for 13 weeks (NTP 1993).

An intermediate-duration oral MRL of 0.01 mg Cu/kg/day was derived for copper based on gastrointestinal effects using the data from the Araya et al. (2003b) study. This study identified NOAEL and LOAEL values of 0.042 and 0.091 mg Cu/kg/day, respectively; these copper doses were in excess of normal dietary intake. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an intermediate-duration oral MRL of 0.01 mg Cu/kg/day. As with the acute-duration MRL, the intermediate-duration MRL is intended to protect against exposure to excess copper in drinking water and assumes a normal copper dietary intake.

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