Copper

This Document is based, in part, on the International Programme on Chemical Safety monograph on Copper (WHO, 1998a), Copper in the *Guidelines for Drinking-Water Quality* (WHO, 1998b), the National Research Council report: *Copper in Drinking Water* (NRC, 2000), the Institute of Medicine Dietary Reference Intakes for Copper (IOM 2001) and *Copper in Society and the Environment* by the Swedish Environmental Research Group (Landner and Lindestrom, 1999).

1. GENERAL DESCRIPTION

1.1 Identity

Paragraph 1

Copper (CAS no. 7440-50-8) is a transition metal that is stable in its metallic state and forms monovalent (cuprous) and divalent (cupric) cations. Copper is both an essential nutrient and a drinking water contaminant of concern. Common copper compounds include the following:

Compound	CAS no.
Copper(II) acetate monohydrate [$Cu(C_2H_3O_2)_2 \cdot H_2O$]	6046-93-1
Copper(II) chloride [$CuCl_2$]	7447-39-4
Copper(II) nitrate trihydrate [$Cu(NO_3)_2 \cdot 3H_2O$]	10031-43-3
Copper(II) oxide [CuO]	1317-38-0
Copper(II) sulfate pentahydrate [$CuSO_4 \cdot 5H_2O$]	7758-99-8

1.2 Physicochemical properties (ATSDR, 1990; Lewis, 1993; Lide, 1995)

Paragraph 1

Compound	Density (g/cm^3)	Water solubility (g/L)
Copper(II) acetate monohydrate	1.88	72
Copper(II) chloride	3.39	706
Copper(II) nitrate trihydrate	2.32	1378
Copper(II) oxide	6.32	Insoluble
Copper(II) sulfate pentahydrate	2.28	316

1.3 Organoleptic properties

Paragraph 1

Dissolved copper imparts a light blue or blue-green color and an unpleasant metallic, bitter taste to drinking-water. The concentration at which 50% of 61 volunteers could detect the taste of copper (taste threshold) as the sulfate or chloride salt in tap or demineralized water ranged from 2.4 to 2.6 mg/L (Zacarias et al., 2001). The taste threshold increased in the presence of other solutes (Olivares & Uauy, 1996a; Zacarias et al., 2001). Blue to green staining of porcelain sinks and plumbing fixtures occurs from copper dissolved in tap-water.

1.4 Major uses

Paragraph 1

Metallic copper is malleable, ductile, and a good thermal and electrical conductor. It has many commercial uses because of its versatility. Copper is used to make electrical wiring, pipes, valves, fittings, coins, cooking utensils, and building materials. It is present in munitions, alloys (brass, bronze), and coatings. Copper compounds are used as or in fungicides, algicides, insecticides, wood preservatives, electroplating, azo dye manufacture, engraving, lithography, petroleum refining, and pyrotechnics. Fertilizers, animal feeds, and pharmaceuticals can contain copper compounds (ATSDR, 1990; Lewis, 1993). Copper compounds are also used as food additives (e.g., nutrient and/or coloring agent) (FDA, 1994). Copper sulfate pentahydrate is sometimes added to surface water for the control of algae (NSF, 2000). Copper sulfate was once prescribed as an emetic, but this use has been discontinued owing to adverse health effects (Ellenhorn & Barceloux, 1988).

1.5 Environmental fate

Paragraph 1

The fate of elemental copper in water is complex and influenced by pH, dissolved oxygen, and the presence of oxidizing agents and chelating compounds or ions (US EPA, 1995). Surface oxidation of copper produces copper(I) oxide or hydroxide. In most instances, copper(I) ion is subsequently oxidized to copper(II) ion. However, copper(I) ammonium and copper(I) chloride complexes, when they form, are stable in aqueous solution.

Paragraph 2

In pure water, the copper(II) ion is the more common oxidation state (US EPA, 1995) and will form complexes with hydroxide and carbonate ions. The formation of insoluble malachite [$Cu_2(OH)_2CO_3$] is a major factor in controlling the level of free copper(II) ion in aqueous solutions. Copper(II) ion is the major species in water at pHs up to 6; at pH 6–9.3, aqueous $CuCO_3$ is prevalent; and at pH 9.3–10.7, the aqueous $[Cu(CO_3)_2]^{2-}$ ion predominates (Stumm & Morgan, 1996).

Paragraph 3

Dissolved copper ions are removed from solution by sorption to clays, minerals, and organic solids or by precipitation. Copper strongly adsorbs to clay materials in a pH-dependent fashion and adsorption is increased by the presence of particulate organic materials (Barceloux, 1999; Landner & Lindestrom, 1999). Copper discharged to

wastewater is concentrated in sludge during treatment. Sorption can be reversed in a reducing or acidic environment; thus, sediments and sludge can act as a reservoir for copper ions. Copper ions are chelated by humic acids and polyvalent organic anions (Landner & Lindestrom, 1999). The presence of chelating agents increases the solubility of copper in an aqueous medium.

2. ANALYTICAL METHODS

Paragraph 1

The most important analytical methods for the detection of copper in water are atomic absorption spectrometry (AAS) with flame detection, graphite furnace atomic absorption spectroscopy, inductively coupled plasma atomic emission spectroscopy, inductively coupled plasma mass spectrometry (ICP-MS), and stabilized temperature platform graphite furnace atomic absorption (ISO, 1986, 1996; ASTM, 1992, 1994; US EPA, 1994). The ICP-MS technique has the lowest detection limit (0.02 µg/L) and the AAS technique, the highest (20 µg/L). Detection limits for the other three techniques range from 0.7 to 3 µg/L. Measurement of dissolved copper requires sample filtration; results from unfiltered samples include dissolved and particulate copper. Simple colorimetric methods are available for measuring copper but should not be used if method sensitivity is required (WHO, 1998a). The USEPA has established 50 µg/L as the practical quantification limit for copper (USEPA, 1991).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Paragraph 1

Copper is present in the atmosphere from wind dispersion of particulate geological materials and particulate matter from smokestack emissions. Collectively these sources account for only 0.4% of the copper released into the environment (Barceloux, 1999). In a nationwide study by the US EPA for the years 1977–1983, the range of copper concentrations in 23,814 air samples was 0.003–7.32 µg/m^3 (US EPA, 1987). Concentrations of copper determined in over 3,800 samples of ambient air from 29 sites in Canada during 1984-1993 averaged 0.014 µg/m^3 (WHO, 1998a). The maximum value was 0.418 µg/m^3). Atmospheric copper is removed by gravitational settling, dry disposition, rain, and snow.

3.2 Water

Paragraph 1

Copper is found in surface water, groundwater, seawater, and drinking-water (ATSDR, 1990; US EPA, 1991). In a 1969 survey of 678 groundwater supplies in the USA, the maximum reported copper concentration was 0.47 mg/L, whereas the mean concentration in samples exceeding the detection limit (0.010 mg/L) was 0.075 mg/L (US EPA, 1991). Comparative values for 109 surface water supplies were 0.304 and 0.066 mg/L, respectively. In the United Kingdom, the mean copper concentration in the River Stour was 0.006 mg/L (range 0.003–0.019 mg/L). Background levels derived from an upper

catchment control site were 0.001 mg/L. Fourfold increases in copper concentrations were apparent downstream of a sewage treatment plant (WHO, 1998a). In an unpolluted zone of the River Periyar in India, copper concentrations ranged from 0.0008 to 0.010 mg/L (WHO, 1998a).

Paragraph 2

Copper concentrations in drinking-water vary widely as a result of variations in pH, hardness, and copper availability in the distribution system. Results from a number of studies from Europe, Canada, and the United States indicate that copper levels in drinking-water can range from ≤0.005 to >30 mg/L, with the primary source most often being the corrosion of interior copper plumbing (US EPA, 1991; Health Canada, 1992; NRC, 2000; WHO, 1998a). Levels of copper in running or fully flushed water tend to be low, whereas those of standing or partially flushed water samples are more variable and can be substantially higher (frequently >1 mg/L) (ATSDR, 1990; WHO, 1998a). Copper concentrations in treated water often increase during distribution, especially in systems with an acid pH or high carbonate-waters with an alkaline pH (US EPA, 1995). In the United States, first-draw copper concentrations (after a minimum six-hour static period) must be reported to the US EPA if they exceed 1.3 mg/L. The median values for first-draw 90th percentile exceedances from 1991 to 1999 were slightly greater than 2 mg/L (7,307 samples). Ten percent of the samples had concentrations exceeding 5 mg/L and 1% were greater than 10 mg/L (NRC, 2000). In 1990/92, the mean copper content of freshly flushed drinking water in German households with a central water supply was 182 µg/l. The mean Cu-content of tap water from single wells was 134 µg/l. The highest value measured in freshly flushed, centrally distributed tap water was 4.8 mg/L and in tap water from single wells 2.8 mg/L (Umwelt-Survey/Environmental Survey, 1990/92).

3.3 Food

Paragraph 1

Food is a principal source of copper exposure for humans. Liver and other organ meats, seafood, nuts, and seeds (including whole grains) are good sources of dietary copper (IOM, 2001). Based on the results of the US Department of Agriculture 1989-1991 survey of food consumption, about 40% of the dietary copper comes from yeast breads, white potatoes, tomatoes, cereals, beef, and dried beans and lentils (Subar et al., 1998). Vitamin/mineral preparations for children and adults generally contain 2 mg of copper per tablet or capsule, most often as copper oxide. Infant formula contains 0.6–2 µg of copper per kcal (Olivares & Uauy, 1996b).

Paragraph 2

Based on data collected during the US Food and Drug Administration's Total Diet Study (1982–1991), the average dietary intake of copper for adult males was 1.1 mg/day, whereas that for adult females was 0.8 to 0.9 mg/day. The average intake for infants (6 months to 1 year) was 0.42 mg/day, and that for 2-year-olds was 0.55 mg/day (Pennington & Schoen, 1995). In Scandinavian countries, copper intakes are in the range of 1.0–2.0 mg/day for adults, 2 mg/day for lactovegetarians, and 3.5 mg/day for vegans (Pettersson

& Sandstrum, 1995; WHO, 1998a). The United Kingdom reported intakes of 1.2 and 1.6 mg/day for adult females and males, respectively, and 0.5 mg/day for children 1½ to 4½ years old. Australia reported intakes of 2.2 and 1.9 mg/day for adult females and males, respectively, and 0.8 mg/day for the 2-year-old. In Germany, the dietary intake of adults was 0.95 mg/day (WHO, 1998a). Surveys in the United States indicate that about 15% of the population uses a nutritional supplement containing copper (IOM, 2001).

Paragraph 3

Copper is an essential nutrient. The United States and Canada recently established a Recommended Dietary Allowance (RDA) for adults of 900 µg/day. Values for children are 340 µg/day for the first three years, 440 µg/day for ages 4 through 8, 700 µg/day for ages 9 through 13, and 890 µg/day for ages 14 through 18 (IOM, 2001). During pregnancy and lactation 1,000 µg/day and 1,300 µg/day are recommended, respectively. Although the data were not sufficient to establish RDAs for infants, based on the copper in human milk, the IOM (2001) estimated that intakes of 200 µg/day were adequate for the first six months and 220 µg/day for the second six months. WHO estimated that average copper requirements are 12.5 µg/kg of body weight per day for adults and about 50 µg/kg of body weight per day for infants (WHO, 1996). The IOM (2001) recommended 10 mg/day as an Tolerable Upper Intake Level (UL) for adults from foods and supplements. In most foods, copper is present bound to proteins rather than as a free ion.

3.4 Estimated total exposure and relative contribution of drinking-water

Paragraph 1

Food and water are the primary sources of copper exposure in developed countries. In general, dietary copper intakes for adults range from 1 to 3 mg/day (WHO, 1998a; IOM, 2001); use of a vitamin/mineral supplement will increase exposure by about 2 mg/day. Drinking-water contributes 0.1–1 mg/day in most situations. Thus, daily copper intakes for adults usually range from 1 to 5 mg/day. Consumption of standing or partially flushed water from a distribution system that includes copper pipes or fittings can considerably increase total daily copper exposure, especially for infants fed formula reconstituted with tap-water.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Paragraph 1

After oral exposure in mammals, absorption of copper occurs primarily in the upper gastrointestinal tract and is controlled by a complex homoeostatic process that apparently involves both active and passive transport (Linder & Hazegh-Azam, 1996; Camakaris et al., 1999; Peña et al., 1999). Mucosal and serosal transport mechanisms are thought to differ, the former relying principally upon facilitated transport, while the latter is mediated by saturable, energy-dependent mechanisms that appear rate-limiting for typical copper intakes (Linder & Hazegh-Azam, 1996). Uptake of copper from the intestines is

susceptible to competitive inhibition by other transition metals (particularly zinc or iron). The presence of dietary proteins and amino acids, complexing or precipitating anions, fructose, ascorbic acid, phytate, fulvic acid, and fiber may also influence copper uptake from the gastrointestinal tract (Lönnerdal, 1996; WHO, 1998a; IOM, 2001).

Paragraph 2

Copper absorption in 11 young male adults was investigated at three dietary levels in initial (0.785, 1.68, or 7.53 mg/day) and follow-up (0.38, 0.66, or 2.49 mg/day) studies by Turnlund et al. (1989, 1998). Apparent absorption was found to vary inversely with dietary intake (ranging from 67% at 0.38 mg/day to 12% at 7.53 mg/day). However, in the 1998 study, actual absorption was more consistent (77%, 73%, and 66% respectively) with increased biliary excretion of the copper at the higher doses accounting for most of the apparent difference in absorption (Turnlund, 1998). Developmental age may influence copper absorption, although data from infants are limited (Zlotkin et al., 1995; Lönnerdal, 1996, 1997,). Intestinal absorption is high in the neonatal rat, but decreases by the time of weaning. More copper is transported to the liver and less remains in the intestine with increasing postnatal age (Lönnerdal, 1996).

Paragraph 3

Within the mucosal cells, most of the copper is found in the cytosol bound to proteins, including copper chaperones (transport proteins) and metallothionein (a storage protein for copper and other metal ions). Copper transport in cells is a tightly regulated process involving a series of copper-binding proteins which protect against free radicle reactions initiated by Cu^{+1}/Cu^{+2} oxidation/reduction reactions (Peña et al., 1999). Serosal transport from the mucosal cells is mediated by a *p*-type ATPase active transport system, which is inhibited in Menkes syndrome, one of several genetic diseases related to copper. Copper in the portal blood is bound to albumin or transcuprin; a small amount may be chelated by peptides and amino acids, especially histidine (Camakaris et al., 1999; Linder & Hazegh-Azam, 1996).

Paragraph 4

Copper uptake from the blood by the liver and distribution within the liver are not completely understood. They are presumed to involve a transport process that differs from that in the intestines (Linder & Hazegh-Azam, 1996). Within the liver, copper becomes incorporated in ceruloplasmin, superoxide dismutase and cytochrome oxidase. Specific copper chaperones deliver copper from the plasma membrane to each of these important cuproenzymes (Peña et al., 1999). A specific p-type ATPase, which is defective in Wilson's disease, is involved with the incorporation of copper in ceruloplasmin and contributes to copper export via bile (Camakaris et al., 1999). Excess copper is bound to hepatic metallothionein (NRC, 2000).

Paragraph 5

In posthepatic circulation, copper is bound to ceruloplasmin, albumin, transcuprin, and to a lesser extent, to certain amino acids such as histidine. Ceruloplasmin is the primary copper transport protein in systemic circulation and contains about 75% of the plasma copper (Luza & Speisky, 1996). It also has enzymatic activity as a ferrooxidase and functions in

the synthesis of hemoglobin. Neither ceruloplasmin nor albumin are apparently required for normal distribution of copper to nonhepatic tissues based upon normal tissue levels of copper in patients with aceruloplasminemia (Peña et al., 1999) and in analbuminemic rats (Linder & Hazegh-Azam, 1996).

Paragraph 6

Excluding hair and nails, the highest concentrations of copper under normal conditions are found in the liver, brain, heart, and kidneys, with moderate concentrations found in the intestine, lung, and spleen (Evans, 1973; Linder & Hazegh-Azam, 1996; Luza & Speisky, 1996; Barceloux, 1999). In healthy adults, the liver contains 8-10% of the body's total copper, while approximately 50% is found in muscle and bone due to their large tissue masses. In newborn infants, however, the liver contains 50-60% of the body's copper (Luza & Speisky, 1996).

Paragraph 7

Copper is required for the proper functioning of many important enzyme systems. Copper-containing enzymes include ceruloplasmin, superoxide dismutase, cytochrome-c oxidase, tyrosinase, monoamine oxidase, lysyl oxidase, and phenylalanine hydroxylase (Linder & Hazegh-Azam, 1996). The activity of the enzyme superoxide dismutase, ceruloplasmin and serum copper concentrations can be used in the assessment of copper status (IOM, 2001). Platelet copper concentration and platelet cytochrome-c oxidase activity may be more sensitive indicators of marginal copper status than the more traditional assessment parameters listed above, but require additional evaluation (IOM, 2001).

Paragraph 8

Copper is excreted from the body in bile, feces, sweat, hair, menses, and urine (Luza & Speisky, 1996; Cox, 1999). In humans, the major excretory pathway for absorbed copper is bile, where copper is bound to both low-molecular-weight and macromolecular species. Biliary export seems to involve glutathione-dependant and glutathione-independent processes (NRC, 2000). Biliary copper is discharged to the intestine where, after minimal reabsorption, it is eliminated in the feces. In normal humans, less than 3% of the daily copper intake is excreted in the urine (Luza & Speisky, 1996). Excretion of endogenous copper in bile may be even more important than absorption in regulating total body level of copper (Turnlund et al., 1998).

Paragraph 9

There are several genetic disorders that affect copper utilization. The genetic abnormalities associated with Menkes syndrome (a deficiency disorder) and Wilson's disease (a toxicity disorder) have been identified as defects in *p*-type ATPases (NRC, 2000). There is some evidence to suggest that an autosomal recessive gene may be a predisposing factor for copper-related cases of infant or childhood cirrhosis (Muller et al., 1996; Tanner, 1999).

Paragraph 10

In Menkes syndrome, and its milder variant Occipital Horn Syndrome, there is minimal copper absorption from the intestines, leading a deficiency state that is independent of copper intake and often leads to death during early childhood (NRC, 2000). Children suffering from Menkes syndrome, an X chromosome-linked disorder, exhibit mental

deterioration, failure to thrive, hypothermia, and connective tissue abnormalities (Harris & Gitlin, 1996). The defective *p*-type ATPase is responsible for serosal transport of copper from intestinal mucosal cells and transport across the blood brain barrier (Camakaris et al., 1999). A child with Menkes syndrome suffers from a profound copper deficiency, despite adequate dietary copper. There is no effective treatment for Menkes syndrome, although administration of copper as the dihistidine complex delays the development of symptoms (Linder & Hazegh-Azam, 1996).

Paragraph 11

Wilson's disease is an autosomal recessive disorder that leads to copper toxicity because it affects the hepatic intracellular transport of copper and its subsequent inclusion into ceruloplasmin and bile. A *p*-type ATPase is again affected, but the enzyme is different from that affected in Menkes syndrome. As is the case with Menkes disease there are a number of genetic variants of this disorder (NRC, 2000). Because copper is not incorporated into ceruloplasmin, its normal systemic distribution is impaired, and copper accumulates in the liver, brain, and eyes (Harris & Gitlin, 1996). Wilson's disease generally appears in late childhood and is accompanied by hepatic cirrhosis, neurologic degeneration, and copper deposits in the cornea of the eye (Kayser-Fleischer rings). Patients with Wilson's disease are treated with chelating agents, such as penicillamine, to promote copper excretion (Yarze et al., 1992). Patients that follow their therapeutic regime can expect to live a normal life (Scheinberg & Sternleib, 1996). Restriction of dietary copper alone cannot influence the progression of the disease.

Paragraph 12

There is some evidence that asymptomatic carriers of a defective Wilson's disease gene also have abnormal hepatic retention of dietary copper (Brewer & Yuzbasian-Gurkan, 1992). However, the data supporting this hypothesis are limited; heterozygous carriers are estimated to occur with a frequency of 1 in 100 individuals (WHO, 1998a) and, thus, are a population of concern.

Paragraph 13

Aceruloplasminemia is an autosomal recessive disorder caused by changes in the ceruloplasmin gene that affect the ability of ceruloplasmin to bind copper (Harris & Gitlin, 1996). The symptoms of aceruloplasminemia do not become apparent until adulthood. They include dementia, diabetes, retinal degeneration, and increased tissue iron stores. Individuals with aceruloplasminemia have apparently normal copper transport and tissue uptake despite the lack of ceruloplasmin (Peña et al., 1999).

Paragraph 14

The etiologies of Indian childhood cirrhosis, Tyrolean infantile cirrhosis, and idiopathic copper toxicosis are complex and may involve a combination of genetic, developmental, and environmental factors (Muller et al., 1996; Pandit & Bhave, 1996; Tanner, 1999; NRC, 2000). These disorders are characterized by liver enlargement, elevated copper deposits in liver cells, pericellular fibrosis, and necrosis and are generally fatal. Poor biliary excretion of copper may play a role in the etiology of the disease.