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Copper

SUMMARY

Copper functions as a component of a number of metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. The primary criterion used to estimate the Estimated Average Requirement (EAR) for copper is a combination of indicators, including plasma copper and ceruloplasmin concentrations, erythrocyte superoxide dismutase activity, and platelet copper concentration in controlled human depletion/repletion studies. The Recommended Dietary Allowance (RDA) for adult men and women is 900 µg/day. The median intake of copper from food in the United States is approximately 1.0 to 1.6 mg/day for adult men and women. The Tolerable Upper Intake Level (UL) for adults is 10,000 µg/day (10 mg/day), a value based on protection from liver damage as the critical adverse effect.

BACKGROUND INFORMATION

Function

The biochemical role for copper is primarily catalytic, with many copper metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. Many copper metalloenzymes have been identified in humans (da Silva and Williams, 1991; Harris, 1997).

Amine oxidases participate in important reactions that have markedly different effects. Diamine oxidase inactivates histamine

released during allergic reactions. Monoamine oxidase (MAO) is important in serotonin degradation to excretable metabolites and in the metabolism of catecholamines (epinephrine, norepinephrine, and dopamine). MAO inhibitors are used as antidepressant drugs. Lysyl oxidase uses lysine and hydroxylysine found in collagen and elastin as substrates for posttranslational processing to produce cross-linkages needed for the development of connective tissues, including those of bone, lung, and the circulatory system.

Ferroxidases are copper enzymes found in plasma, with a function in ferrous iron oxidation ($\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$) that is needed to achieve iron's binding to transferrin (Linder and Hazegh-Azam, 1996). Ferroxidase I, also called ceruloplasmin, is the predominant copper protein in plasma and may also have antioxidant functions. Defects in ceruloplasmin function produce cellular iron accumulation, a result that supports its ferroxidase role (Harris and Gitlin, 1996). Ferroxidase II is found in human plasma, but it may have a role in iron metabolism in specific cellular sites. A transmembrane copper-containing protein (hephaestin) with ferroxidase activity has been described (Pena et al., 1999; Vulpe et al., 1999). Cytochrome *c* oxidase is a multisubunit enzyme in mitochondria that catalyzes reduction of O_2 to H_2O . This establishes a high energy proton gradient required for adenosine triphosphate (ATP) synthesis. This copper enzyme is particularly abundant in tissues of greatest metabolic activity including heart, brain, and liver. Dopamine β monooxygenase uses ascorbate, copper, and O_2 to convert dopamine to norepinephrine, a neurotransmitter, produced in neuronal and adrenal gland cells. Dopa, a precursor of dopamine, and metabolites used in melanin formation are oxidatively produced from tyrosine by the copper enzyme tyrosinase. α -Amidating monooxygenase (α -AE), also called peptidylglycine α -AE, uses copper and ascorbate to remove two carbons from a C-terminal glycine of peptides, thus generating an amide. A number of peptide hormones are posttranslationally modified by α -AE (Harris, 1997).

Two forms of superoxide dismutase are expressed in mammalian cells, a manganese and cupro/zinc form (Harris, 1997). Copper/zinc superoxide dismutase (Cu/Zn SOD) uses two copper atoms for conversion of the superoxide anion (O_2^-) to H_2O_2 and O_2 . Zinc atoms have a structural role in the enzyme. The enzyme is localized in the cytosol and, along with the mitochondrial manganese-containing form, provides a defense against oxidative damage from superoxide radicals that, if uncontrolled, can lead to other damaging reactive oxygen species. Mutations in the Cu/Zn SOD gene, which alter the

protein's redox behavior, produce amyotrophic lateral sclerosis (Lou Gehrig's disease).

These are the principal copper metalloenzymes found in humans. There is substantial documentation from animal studies that diets low in copper reduce the activities of many of these copper metalloenzymes. Activities of some copper metalloenzymes have been shown to decrease in human copper depletion (Milne, 1994; Turnlund, 1999). Physiologic consequences resulting from copper deficiency include defects in connective tissue that lead to vascular and skeletal problems, anemia associated with defective iron utilization, and possibly specific aspects of central nervous system dysfunction (Harris, 1997; Turnlund, 1999). Some evidence suggests that immune and cardiac dysfunction occurs in experimental copper deficiency and the development of such signs of deficiency has been demonstrated in infants (Graham and Cordano, 1969; Olivares and Uauy, 1996; Turnlund, 1999).

Physiology of Absorption, Metabolism, and Excretion

Metabolism of copper in humans relies on the intestine for control of homeostasis as the capacity for renal copper excretion is limited. Nearly two-thirds of the body copper content is located in skeleton and muscle, but studies with stable isotopes have shown that the liver is a key site in maintaining plasma copper concentrations (Olivares and Uauy, 1996; Turnlund et al., 1998). Copper has a higher binding affinity for proteins than all other divalent trace elements (da Silva and Williams, 1991). Consequently, precise control of intracellular copper trafficking is needed to regulate how it is donated to appropriate sites.

Copper absorption occurs primarily in the small intestine. Some absorption may occur in the stomach where the acidic environment promotes copper solubility by dissociation from copper-containing macromolecules derived from dietary sources (Harris, 1997; Turnlund, 1999). Both saturable-mediated and nonsaturable-nonmediated (possibly paracellular) transepithelial copper movements have been reported. The Menkes P-type ATPase (MNK; ATP7A) is believed to be responsible for copper trafficking to the secretory pathway for efflux from cells, including enterocytes (Harris and Gitlin, 1996). A defective MNK gene causes Menkes' disease, which is characterized by reduced copper absorption and placental copper transport. The extent of copper absorption varies with dietary copper intake (Turnlund, 1998). It ranges from over 50 percent at an intake of less than 1 mg/day to less than 20 percent above 5 mg/day. About

35 percent of a 2 mg/day intake is absorbed and is transported via the portal vein to the liver, bound to albumin, for uptake by liver parenchymal cells.

Biliary copper excretion is adjusted to maintain balance. Copper is released via plasma to extrahepatic sites where up to 95 percent of the copper is bound to ceruloplasmin (Turnlund, 1999). The biological role of ceruloplasmin in copper metabolism has been widely investigated. The autosomal recessive disorder in humans, aceruloplasminemia, does not produce abnormal copper metabolism, thus contradicting a role for the protein in copper delivery to cells. However, this genetic defect results in tissue iron accumulation, supporting the protein's role in cellular iron release. Other P-type ATPases (e.g., Wilson, NND, ATP7B) are responsible for copper trafficking to the secretory pathway for ceruloplasmin synthesis or for endosome formation before transport into the bile (Harris and Gitlin, 1996; Pena et al., 1999). Mutations of this copper-transporting ATPase result in cellular copper accumulation called Wilson's disease. Urinary copper excretion is normally very low (< 0.1 mg/day) over a wide range of dietary intakes (Turnlund, 1999). As with other trace elements, renal dysfunction can lead to increased urinary losses.

Clinical Effects of Inadequate Intake

Frank copper deficiency in humans is rare, but has been found in a number of special conditions. It has been observed in premature infants fed milk formulas, in infants recovering from malnutrition associated with chronic diarrhea and fed cow's milk (Shaw, 1992), and in patients with prolonged total parenteral nutrition (Fujita et al., 1989). In these cases, serum copper and ceruloplasmin concentrations were as low as 0.5 μmol and 35 mg/L, respectively, compared to reported normal ranges of 10 to 25 $\mu\text{mol/L}$ for serum copper concentration and 180 to 400 mg/L for ceruloplasmin concentration (Lentner, 1984). Supplementation with copper resulted in rapid increases in serum copper and ceruloplasmin concentrations.

Symptoms accompanying the copper deficiency included normocytic, hypochromic anemia, leukopenia, and neutropenia (Fujita et al., 1989). Osteoporosis was observed in copper-deficient infants and growing children.

Copper deficiency developed in six severely handicapped patients between the ages of 4 and 24 years who were fed an enteral diet containing 15 μg of copper/100 kcal for 12 to 66 months (Higuchi

et al., 1988). Their serum copper concentrations ranged from 0.9 to 7.2 $\mu\text{mol/L}$ and ceruloplasmin concentrations ranged from 30 to 125 mg/L . Two patients had neutropenia, one had macrocytic, normochromic anemia, and some had bone abnormalities including reduced bone density. Neutrophil counts normalized and bone abnormalities improved after copper supplementation. If the copper intake of these patients is extrapolated to adults on the basis of caloric intake, copper deficiency might be expected to develop in adults at an intake of 440 $\mu\text{g}/2,900$ kcal for men and 290 $\mu\text{g}/1,900$ kcal for women. This deduction is consistent with a study in which healthy young men who were fed a diet containing 380 $\mu\text{g}/\text{day}$ of copper for 42 days had a decline in serum copper and ceruloplasmin concentrations and then an increase with copper repletion (Turnlund et al., 1997). Although serum copper and ceruloplasmin concentrations of these men did not fall to the deficient range in 42 days and clinical symptoms did not appear, these effects might be expected had the low copper diet been continued. In a number of other studies at higher levels of copper intake (i.e., at 600 $\mu\text{g}/\text{day}$ and above), serum copper and ceruloplasmin concentrations did not decline significantly (Milne, 1998; Turnlund et al., 1990).

Results of depletion studies in laboratory animals have led to interest in a number of conditions in humans that may be associated with marginal copper intake over a long period. Insufficient data are available at this time to establish whether these conditions are related to dietary copper.

A report of increased blood cholesterol concentrations in one young man consuming 830 $\mu\text{g}/\text{day}$ of copper (Klevay et al., 1984) suggested that elevated blood cholesterol concentration may be associated with marginal amounts of dietary copper. This effect was not observed in other subjects or in a number of other studies with this or lower levels of dietary copper. In one study, blood cholesterol concentration decreased with lower dietary copper (Milne and Nielsen, 1996), and in a copper supplementation study investigators found increased blood cholesterol concentrations with supplementation (Medeiros et al., 1991).

Heart beat irregularities were reported in some studies, and investigators linked them to dietary copper intake (Milne, 1998). However, heart beat irregularities are common in normal, healthy people, and other studies with lower copper intake demonstrated that such irregularities, monitored during copper depletion and repletion, were common at all intake levels of dietary copper (Turnlund et al., 1997). Myocardial disease occurs in severely deficient weanling rats, and one investigator has hypothesized that ischemic heart disease is

related to marginal copper status (Klevay, 1989). However, the myocardial changes observed in copper-deficient animals are very different from those of ischemic heart disease in humans (Danks, 1988). In severely deficient animals, the myocardium is hypertrophied and may rupture. Coronary artery resistance is decreased in copper-deficient animals, but it is increased in ischemic heart disease.

Several other clinical observations deserve further investigation, but there is insufficient evidence to link them to marginal copper status. Glucose tolerance was lower in two of a group of eight men consuming 80 $\mu\text{g}/\text{day}$ of copper than in men consuming higher levels of copper (Klevay et al., 1986), but similar observations have not been reported at lower intakes of copper in other studies. One study reported a negative correlation between ceruloplasmin concentration and blood pressure during a hand grip exercise (Lukaski et al., 1988), but the link between blood pressure and dietary copper has not been investigated further in humans. An index of immune function declined in a depletion study with copper intakes of 380 $\mu\text{g}/\text{day}$ that resulted in decreases in indexes of copper status, but other indexes of immune function did not decline and repletion did not result in reversal of the change (Kelley et al., 1995). Changes in blood clotting factors V and VIII were observed in one study with copper intakes of 570 $\mu\text{g}/\text{day}$ (Milne and Nielsen, 1996). The role of copper as an antioxidant has led to interest in the possibility that copper deficiency impairs antioxidant status (Johnson et al., 1992). A report of changes in some, but not other, markers of bone metabolism with a dietary copper intake of 700 $\mu\text{g}/\text{day}$ deserves further investigation (Baker et al., 1999). Changes in catecholamine metabolism have been investigated, but results are inconsistent (Bhathena et al., 1998).

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR COPPER

Several indicators are used to diagnose copper deficiency. These indicators—serum or plasma copper concentration, ceruloplasmin concentration, and erythrocyte superoxide dismutase activity—are low with copper deficiency and respond to copper supplementation. However, except when diets are deficient in copper, they do not reflect dietary intake and may not be sensitive to marginal copper status. In addition, serum copper and ceruloplasmin concentrations increase during pregnancy and with a number of diseases, and therefore copper deficiency could be masked under these

conditions. Platelet copper concentration and cytochrome *c* oxidase activity may be more sensitive to marginal intakes of dietary copper than plasma copper or ceruloplasmin concentration, but they have been measured in very few studies to date. No single indicator provides an adequate basis on which to estimate the copper requirement.

Serum Copper Concentrations

Serum copper concentration is a reliable indicator of copper deficiency, falling to very low concentrations in copper-deficient individuals. The lower end of the normal range for serum copper concentration is reported to be 10 $\mu\text{mol/L}$, but serum copper concentrations were considerably lower than this when cases of copper deficiency were discovered. Serum copper concentration returns to normal within a few days of copper supplementation (Danks, 1988). While serum copper concentration is an index of copper deficiency, it does not reflect dietary intake except when intake is below a certain level. Above this level, supplementation with copper does not increase serum copper concentration. Serum copper concentration increases under a number of conditions due to increased concentrations of ceruloplasmin.

Ceruloplasmin Concentration

Ceruloplasmin concentration is also a reliable indicator of copper deficiency. Ceruloplasmin carries between 60 and 95 percent of serum copper, and changes in serum copper concentration usually parallel the ceruloplasmin concentration in the blood. Ceruloplasmin, too, falls to low concentrations with copper deficiency, far below the lower end of the normal range of 180 mg/L , and it responds quickly to repletion (Danks, 1988). Ceruloplasmin does not respond to dietary intake, unless intake is very low. The dietary copper intake at which ceruloplasmin concentration no longer increases in response to increased dietary copper might be considered the copper requirement for ceruloplasmin synthesis. Ceruloplasmin is an acute phase protein and increases markedly with a number of diseases, including liver disease, malignancy, inflammatory diseases, myocardial infarction, and a variety of infectious diseases (Mason, 1979). It also increases with pregnancy and oral contraceptive use. With any of these conditions, copper deficiency might not be diagnosed on the basis of serum copper or ceruloplasmin concentrations.

Erythrocyte Superoxide Dismutase Activity

Erythrocyte superoxide dismutase (SOD) activity, though not as specific as serum copper or ceruloplasmin concentration, may be a reliable indicator of copper status, and some suggest it is more sensitive (Milne, 1998; Uauy et al., 1985). It does not increase with the conditions that increase serum copper and ceruloplasmin concentrations. However, it can increase in situations that produce oxidative stress, and SOD activity is high in some conditions, including alcoholism and Down's syndrome. Methods of analysis are not standardized, and normal ranges for SOD activity are not available. Although SOD activity was measured in fewer studies than were the two indicators above, sufficient data are available to include it as an indicator of change in copper status when it is measured in controlled studies at different levels of dietary copper intake.

*Platelet Copper Concentration and Cytochrome *c* Oxidase Activity*

Two studies in women suggest that both platelet copper concentration and platelet cytochrome *c* oxidase activity may respond more rapidly to low dietary copper than the indicators discussed above. In one study both of these indicators declined when copper intake was 570 $\mu\text{g}/\text{day}$ (Milne and Nielsen, 1996). Platelet copper concentration increased after repletion, but platelet cytochrome *c* oxidase activity did not. In another study, both platelet copper concentration and platelet cytochrome *c* oxidase activity increased after supplementation of a diet containing 670 $\mu\text{g}/\text{day}$ of copper, but baseline measurements were not made, so it is not known whether these parameters declined (Milne et al., 1988). Moreover, an intervening vitamin C supplementation period added another variable to the data interpretation. The fact that serum copper and ceruloplasmin concentrations and SOD activity were not affected at this level of dietary copper suggests the requirement for maintaining serum copper and ceruloplasmin concentration had been met. Therefore, the above research suggests that platelet copper concentration and platelet cytochrome *c* oxidase activity, when measured in controlled studies, may be more sensitive to changes in copper dietary intake.

Urinary Copper

Urinary copper excretion is extremely low and does not contribute significantly to copper retention, but it has been found to decline when diets are low enough in copper that other indexes of

copper status change (Turnlund et al., 1997). Above those levels of dietary intake, urinary copper does not respond to increases in dietary copper. In controlled studies, a decline in urinary copper excretion can be used as supporting evidence for inadequate intake.

Leukocyte Copper Concentration

Leukocyte copper concentration was found to decline along with other indexes of copper status in one study (Turnlund et al., 1997), but it has not been reported in others. Too few data are currently available to use it for establishing dietary recommendations for copper.

Lysyl Oxidase Activity

Lysyl oxidase activity in the skin, which declined with low dietary copper and increased with repletion, is potentially a useful indicator of copper status (Werman et al., 1997). It is not known if lysyl oxidase activity reflects dietary intake at higher levels of dietary copper in humans. Because data are available from only one study, it cannot yet be used as an indicator for estimating copper requirements.

Peptidyl Glycine α -Amidating Monooxygenase Activity

Peptidyl glycine α -amidating monooxygenase (PAM) activity in serum of rats and stimulation of activity are sensitive indicators of copper intake in the rat (Prohaska et al., 1997). Patients with Menkes' disease, who have severe copper deficiency due to a metabolic defect in copper transport, had an increased copper stimulation index of plasma PAM as compared with healthy control subjects. This finding suggests that PAM activity may be a useful indicator of copper status in humans when human dose-response data become available.

Diamine Oxidase Activity

Two copper supplementation studies demonstrated that the activity of serum diamine oxidase (DAO), another cuproenzyme, increases when supplements containing 2 mg (Jones et al., 1997) and 6 mg (Kehoe et al., 2000) of copper were administered daily, a result that suggests the enzyme may be sensitive to increased dietary copper. It has not yet been studied under conditions of copper

depletion. Because intestinal damage and a number of conditions also elevate DAO activity, its use as an indicator of copper status is possibly limited.

Copper Balance

Balance studies have been used in the past to estimate dietary recommendations. Numerous copper balance studies in humans have been conducted over a wide range of intakes (Mason, 1979). Unfortunately, there are a number of problems with this approach, as reviewed by Mertz (1987). Copper balance, which can be achieved over a broad range of dietary copper intakes, reflects prior dietary intake; thus long adaptation is required for results to be meaningful. Seldom are studies long enough. Such studies are prone to numerous errors, and data from some studies would suggest that an unacceptable amount of copper would accumulate over time if these levels of retention were continued. In addition, miscellaneous losses, while small, are very difficult to quantify. Therefore, balance studies were not used as an indicator of copper status.

Factorial Analysis

One approach to estimating minimum dietary mineral requirements is by the factorial method. Obligatory losses, the amounts of an element excreted with no dietary intake, are determined, and then the amount needed in the diet to replace these obligatory losses is calculated. Obligatory losses include urinary losses, gastrointestinal losses, sweat, integument, hair, nails, and other miscellaneous losses such as menstrual and semen losses. For copper, as for other elements, reliable values for many of these losses are not available. However, sufficient data are available to make reasonable estimates; therefore, this method can be used in support of estimates of dietary copper requirements made by other methods.

FACTORS AFFECTING THE COPPER REQUIREMENT

The composition of the diet has little effect on the bioavailability of copper, except in unusual circumstances. The bioavailability of copper is influenced markedly by the amount of copper in the diet. Bioavailability ranges from 75 percent of dietary copper absorbed when the diet contains only 400 µg/day to 12 percent absorbed when the diet contains 7.5 mg/day (Turnlund et al., 1989, 1998). The absolute amount of copper absorbed is higher with increasing

intake. In addition, excretion of copper into the gastrointestinal tract regulates copper retention. As more copper is absorbed, turnover is faster and more copper is excreted into the gastrointestinal tract (Turnlund et al., 1998). This excretion is probably the primary point of regulation of total body copper. This efficient homeostatic regulation of absorption and retention helps protect against copper deficiency and toxicity.

Zinc

Zinc intakes, well in excess of the amount normally found in the diet, can decrease copper absorption in adults (Turnlund, 1999) (see Table 12-7). In one case report, an infant who was given 16 to 24 mg/day of zinc developed copper deficiency (Botash et al., 1992). Very high doses of zinc have been used to treat patients with Wilson's disease, an inborn error of copper metabolism resulting in copper toxicity (Brewer et al., 1983). This zinc-induced inhibition of copper absorption could be the result of competition for a common, apically oriented transporter or the induction of metallothionein in intestinal cells by zinc. Because this protein has a higher binding affinity for copper than for zinc, copper is retained within enterocytes and its absorption is reduced. This response has been used as a therapy to diminish copper absorption in patients with Wilson's disease (Yuzbasiyan-Gurkan et al., 1992). The interaction could also be responsible for reducing copper absorption during consumption of zinc supplements. When zinc-to-copper ratios of 2:1, 5:1, and 15:1 were fed to humans, there were limited effects on copper absorption (August et al., 1989).

Iron

High iron intakes may interfere with copper absorption in infants. Infants fed a formula containing low concentrations of iron absorbed more copper than infants consuming the same formula with a higher iron concentration (Haschke et al., 1986). Such an interaction has been reported to produce reduced copper status in infants (Lonnerdal and Hernell, 1994; Morais et al., 1994).

Fructose

Studies in rats demonstrated that diets very high in fructose were associated with increased severity of copper deficiency in rats (Fields et al., 1984), but a similar effect was not observed in pigs

(Schoenemann et al., 1990), which have cardiovascular systems and gastrointestinal tracts more similar to those of humans. The effects were inconsistent in humans (Reiser et al., 1985) but did not result in copper depletion, and the extremely high levels of fructose fed (20 percent of energy intake) suggest the effect would not be relevant to normal diets.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 through 12 Months

Method Used to Set the Adequate Intake

No functional criteria of copper status have been demonstrated that reflect response to dietary intake in infants. Thus, recommended intakes of copper are based on an Adequate Intake (AI) that reflects the observed mean copper intake of infants principally fed human milk.

Ages 0 through 6 Months. The AI for infants ages 0 through 6 months was based on the usual intake from human milk. The copper content of human milk is highest during early lactation and then declines during the course of lactation. According to a number of reports (Biego et al., 1998; Raiten et al., 1998; Rossipal and Krachler, 1998), the mean copper content of human milk during the first 6 months of lactation is approximately 250 µg/L (Table 7-1). There are no indications that the copper content of human milk is inadequate to maintain copper status. Liver copper stores are high (Widdowson and Dickerson, 1964) and serum copper and ceruloplasmin concentrations are low (Salmenpera et al., 1986) in newborn infants. During the first 6 months of life, liver stores decline and serum copper concentration increases to adult levels, independent of copper intake.

Based on the copper content of human milk and milk consumption (Chapter 2), the AI for infants ages 0 through 6 months is 200 µg/day (250 µg/L × 0.78 L/day) after rounding. For a 7 kg infant (reference weight for 0 through 6 months, Chapter 2), this would be 28 µg/kg/day (200 µg/day/7 kg), rounded up to 30 µg/kg/day.

Ages 7 through 12 Months. One method for estimating the AI for infants receiving human milk, ages 7 through 12 months, is based on the average intake from human milk plus an added increment for complementary foods (Chapter 2). According to the Third

TABLE 7-1 Copper Concentration in Human Milk

Reference	Study Group	Stage of Lactation	Milk Concentration (µg/L)	Estimated Copper Intake of Infants (µg/d) ^a
Picciano and Guthrie, 1976	50 women	6–12 wk	245	190
Vaughan et al., 1979	38 women, 19–42 y	1–3 mo	430	330
		4–6 mo	330	260
		7–9 mo	300	180
		10–12 mo	240	140
		13–18 mo	290	170
		19–31 mo	280	170
Vuori and Kuitunen, 1979	27 women	2 wk	600	470
		20 wk	250	150
Vuori et al., 1980	15 women, 24–35 y	6–8 wk	360	280
		17–22 wk	210	160
Higashi et al., 1982	21 women, 21–35 y	1 mo	450	350
		3 mo	290	230
		5 mo	200	160
Dewey and Lonnerdal, 1983	20 women	1 mo		250
		2 mo		230
		3 mo		220
		4 mo		200
		5 mo		150
		6 mo		200
Fransson and Lonnerdal, 1984	15 milk samples	2–4 mo	320	250
Casey et al., 1985	11 women, 26–39 y	8 d	590	460
		14 d	490	380
		21 d	420	320
		28 d	410	320
Lipsman et al., 1985	7–13 teens	1 mo	350	270
		2 mo	290	230
		3 mo	380	290
		4 mo	280	220
		5 mo	210	160
		6 mo	200	120
		7 mo	190	110

TABLE 7-1 Continued

Reference	Study Group	Stage of Lactation	Milk Concentration (µg/L)	Estimated Copper Intake of Infants (µg/d) ^a
Butte et al., 1987	45 women	1 mo		270
		2 mo		230
		3 mo		210
		4 mo		200
Casey et al., 1989	22 women	7 d	620	480
		5 mo	220	170
Anderson, 1992	7 women	Up to 5 mo	310	240
Anderson, 1993	6 women, 20–30 y		110–380	
Biego et al., 1998	17 milk samples	Mature milk	250	190
Rossipal and Krachler, 1998	46 women	1–3 d	570	440
		42–60 d	230	180
		97–293 d	150	90

NOTE: Maternal intakes were reported in only two studies: in Vaughan et al. (1979), mean intakes (mg/day) were 3.64, 1.90, 2.37, 6.80, and 2.50 at 4–6, 7–9, 10–12, 13–18, and 19–31 months; in Vuori et al. (1980), mean intakes (mg/day) were 1.88 at 6–8 weeks and 1.73 at 17–22 weeks.

^a Copper intake based on reported data or concentration (µg/L) × 0.78 L/day for 0–6 months postpartum and concentration (µg/L) × 0.6 L/day for 7–12 months postpartum.

National Health and Nutrition Examination Survey, the median copper intake from weaning food for children aged 7 through 12 months is 100 µg/day (*n* = 45). The average copper concentration in human milk declines over time, and between 7 and 12 months postpartum the concentration is 200 µg/L or less (Table 7-1). Based on an average volume of 0.6 L/day of human milk that is secreted, the copper intake from human milk is 120 µg/day (0.6 × 200). Therefore the total intake of copper from human milk and complementary foods is 220 µg/day (120 + 100). For a 9 kg infant (reference weight 7 through 12 months, Chapter 2), this would be 24 µg/kg/day (220 µg/kg ÷ 9 kg).

If the AI were extrapolated from the AI for younger infants by using the calculation in chapter 2, the average intake would be 241 µg/day.

Copper AI Summary, Ages 0 through 12 Months

AI for Infants

0–6 months	200 µg/day of copper	30 µg/kg/day
7–12 months	220 µg/day of copper	24 µg/kg/day

Special Considerations

The concentration of copper in cow milk has been reported to range from 60 to 90 µg/L (Fransson and Lonnerdal, 1983) which is lower than that reported for human milk (Table 7-1). Copper is bound to the fat fraction (15 percent) in cow milk with the remaining bound to casein (King et al., 1959). It has been reported that copper absorption in infants fed human milk is greater than in infants fed a cow milk-based formula (Dorner et al., 1989; Johnson and Canfield, 1989). Copper deficiency has been observed in infants fed cow milk (Cordano et al., 1964; Levy et al., 1985). Dorner and coworkers (1989) showed that 20 percent of children were in negative balance when fed unsupplemented formula, whereas all children were in positive balance when fed either human milk or supplemented formula.

Children and Adolescents Ages 1 through 18 Years

Method Used to Estimate the Average Requirement

No data are available on which to base the Estimated Average Requirement (EAR) for copper for children or adolescents. In the absence of additional information, EARs and Recommended Dietary Allowances (RDAs) for children and adolescents have been estimated by using the method described in Chapter 2, which extrapolates from the adult EAR. Although there are no studies available to indicate that the copper requirement is associated with energy expenditure, metabolic weight ($\text{kg}^{0.75}$) was used for extrapolating because of the structural and functional role of copper in a number of enzymes and because using metabolic weight yields an EAR that is higher than when total body weight is used.

Copper EAR and RDA Summary, Ages 1 through 18 Years

EAR for Children

1–3 years	260 µg/day of copper
4–8 years	340 µg/day of copper

EAR for Boys

9–13 years 540 µg/day of copper

14–18 years 685 µg/day of copper

EAR for Girls

9–13 years 540 µg/day of copper

14–18 years 685 µg/day of copper

The RDA for copper is set by using a coefficient of variation (CV) of 15 percent (see Chapter 1 and the discussion of adult requirements that follows) because information is not available on the standard deviation of the requirement for these age groups. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for copper the RDA is 130 percent of the EAR). The calculated RDA is rounded to the nearest 10 µg.

RDA for Children

1–3 years 340 µg/day of copper

4–8 years 440 µg/day of copper

RDA for Boys

9–13 years 700 µg/day of copper

14–18 years 890 µg/day of copper

RDA for Girls

9–13 years 700 µg/day of copper

14–18 years 890 µg/day of copper

Adults Ages 19 Years and Older

Evidence Considered in Estimating the Average Requirement

Biochemical Indicators. No single indicator was judged as sufficient for deriving an EAR for adults. Results for specific indicators vary between studies. To determine the EAR, a combination of indicators was used, including plasma copper concentration, serum ceruloplasmin concentration, erythrocyte superoxide dismutase activity (SOD), and platelet copper concentration in controlled human depletion/repletion studies using specific amounts of copper. If there were significant decreases in serum copper and ceruloplasmin concentrations and SOD activity when the experimental copper diet was fed, and if this decrease was reversed with added copper, then

the experimental diet was considered insufficient to maintain status and therefore deficient in copper. If plasma copper and serum ceruloplasmin concentrations did not change significantly when the experimental diet was fed, but platelet copper concentration decreased, then the experimental diet was judged to be marginally adequate in copper. A lack of change in the copper status indicators indicated that the level of copper in the experimental diet was adequate to maintain status. Because of limited data, data from men and women were combined.

Three studies were used to estimate the average requirement on the basis of copper status. These studies are summarized in Table 7-2. Serum copper and ceruloplasmin concentrations and SOD activity declined significantly in eight of 11 young men fed an experimental, depletion diet containing 388 $\mu\text{g}/\text{day}$ and increased with repletion (Turnlund et al., 1997). Although these indicators decreased significantly, they did not fall to the deficient range while the deficient diet was fed for 42 days. However, it is expected that they would have fallen to the deficient range over a longer time. Other changes suggesting copper depletion were observed.

When young men were fed 790 $\mu\text{g}/\text{day}$ of copper, the above mentioned indicators did not decline significantly (Turnlund et al., 1990). After a decline in copper status, two of the 11 men responded to copper repletion. Therefore, the copper requirement to maintain copper status in half of a group is more than 380 $\mu\text{g}/\text{day}$ but less than 790 $\mu\text{g}/\text{day}$. On the basis of these data, a linear model was used to estimate a response curve. The model estimated that half of these men would not maintain copper status at 550 $\mu\text{g}/\text{day}$.

Serum copper and ceruloplasmin concentrations did not decline significantly when ten women were fed 570 $\mu\text{g}/\text{day}$ of copper (Milne and Nielsen, 1996). Platelet copper concentration, however, declined significantly for eight of ten women fed 570 $\mu\text{g}/\text{day}$ and increased with supplementation. Other indicators did not respond to depletion. Platelet cytochrome *c* oxidase and erythrocyte SOD activity declined but did not respond significantly to repletion. While an EAR based on the first two studies was estimated at 550 $\mu\text{g}/\text{day}$, the latter study suggests that 600 $\mu\text{g}/\text{day}$ may be a marginal intake in over half of the population. Therefore, another increment was added to cover half of the population, and the EAR was set at 700 $\mu\text{g}/\text{day}$.

Factorial Analysis. Another approach for estimating the minimum copper requirement is to estimate obligatory losses of copper and calculate the amount of copper required in the diet to replace these

TABLE 7-2 Effects of Copper (Cu) Intake on Copper Status

Reference	Subjects	Duration of Study	Dietary Cu Intake (mg/d)	Results
Turnlund et al., 1990	11 healthy men	90 d	1.68 × 24 d 0.79 × 42 d 7.53 × 24 d	Plasma Cu, ceruloplasmin, superoxide dismutase (SOD), urinary and salivary Cu: no change due to Cu intake Cu sweat losses very low
Milne and Nielsen, 1996	10 post-menopausal women, aged 49–75 y (mean 63 y)	≈ 6 mo	0.57 × 105 d 2.57 × 35 d (2 mg as supplement)	Urinary Cu: no change throughout study Plasma Cu and ceruloplasmin: no significant change SOD and platelet cytochrome <i>c</i> oxidase: significantly lower after depletion, but no increase during repletion Platelet Cu declined during depletion and increased with repletion
Turnlund et al., 1997	11 healthy men, mean age 26 y	90 d	0.66 × 24 d 0.38 × 42 d 2.49 × 24 d	Plasma Cu, SOD, ceruloplasmin, and urinary Cu declined with depletion and increased with repletion

obligatory losses. This approach provides supporting evidence for the EAR based on copper status estimated above. Endogenous losses, estimated from total parenteral nutrition (TPN) data, were estimated to be 300 µg/day by Shike and coworkers (1981). This estimate was based on gastrointestinal losses from patients without excessive gastrointestinal secretions (less than 0.3 L/day) of 191 µg/day and urinary losses of 90 µg/day, which are higher than urinary losses in normal, healthy adults, and would provide an increment for miscellaneous losses. The TPN patients received no copper orally, but copper from TPN ranged from 250 to 1,850 µg/day.

There are no data on obligatory copper losses in healthy people; therefore the study with the lowest copper intake and data on

endogenous losses was used to estimate obligatory losses in healthy people (Turnlund et al., 1997, 1998). When copper intake was 380 $\mu\text{g}/\text{day}$, copper status declined significantly. Endogenous fecal losses were calculated to be 240 $\mu\text{g}/\text{day}$, slightly higher than the estimate from TPN data (Shike et al., 1981), and urinary losses were less than 20 $\mu\text{g}/\text{day}$. A careful study of surface copper losses in men reported that these averaged 42 $\mu\text{g}/\text{day}$ (Milne et al., 1991). Other losses, such as hair, nails, semen, or menstrual, have not been measured, and it is assumed they are similar to surface losses. Therefore the amount of absorbed copper needed to replace obligatory losses is 344 $\mu\text{g}/\text{day}$ ($240 + 20 + 42 + 42$). Copper absorption at this level of intake is approximately 75 percent. Therefore, 460 $\mu\text{g}/\text{day}$ of dietary copper would be the minimum amount required to replace obligatory losses. Endogenous fecal copper was 50 $\mu\text{g}/\text{day}$ higher at 380 $\mu\text{g}/\text{day}$ than at 460 $\mu\text{g}/\text{day}$, and so 50 $\mu\text{g}/\text{day}$ was added to endogenous fecal losses to account for the increase that occurs between 380 and 460 $\mu\text{g}/\text{day}$. Thus 510 $\mu\text{g}/\text{day}$ ($460 + 50$) of dietary copper is required to replace copper losses from all sources and to achieve zero balance. Estimation of the average requirement based on indicators of copper status is similar to, but slightly higher than, the average requirement determined by the factorial approach. The EAR is based on biochemical indicators of copper status of men and women, and there was no basis for a difference in requirement based on gender. There are no data on which to base an EAR for older adults, and no evidence to suggest that the requirements would be different.

Copper EAR and RDA Summary, Ages 19 Years and Older

EAR for Men

19–50 years	700 $\mu\text{g}/\text{day}$ of copper
51–70 years	700 $\mu\text{g}/\text{day}$ of copper
> 70 years	700 $\mu\text{g}/\text{day}$ of copper

EAR for Women

19–50 years	700 $\mu\text{g}/\text{day}$ of copper
51–70 years	700 $\mu\text{g}/\text{day}$ of copper
> 70 years	700 $\mu\text{g}/\text{day}$ of copper

The data available to set an EAR are limited for men and women, as well as the number of levels of dietary copper in depletion/repletion studies. Thus, a CV of 15 percent is used. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98

percent of individuals in the group (therefore, for copper the RDA is 130 percent of the EAR). The calculated RDA is rounded to the nearest 100 μg .

RDA for Men

19–50 years	900 $\mu\text{g/day}$ of copper
51–70 years	900 $\mu\text{g/day}$ of copper
> 70 years	900 $\mu\text{g/day}$ of copper

RDA for Women

19–50 years	900 $\mu\text{g/day}$ of copper
51–70 years	900 $\mu\text{g/day}$ of copper
> 70 years	900 $\mu\text{g/day}$ of copper

Pregnancy

Evidence Considered in Estimating the Average Requirement

There are no data for establishing an EAR for pregnancy. Therefore, the EAR was based on estimates of the amount of copper that must be accumulated during pregnancy to account for the fetus and products of pregnancy. The full-term fetus contains about 13.7 mg copper (Widdowson and Dickerson, 1964). The copper content of the fetus is high compared to that of adults due to the high concentration of copper in the liver. In addition to the amount of copper accumulated by the fetus, other products that accumulate copper during pregnancy, including placenta amniotic fluid and maternal tissue, should be considered. The concentration of these tissues is lower, about one-third of the concentration of the fetus; therefore another 4.6 mg is added to 13.7 mg for a total of 18 mg copper. Over the course of pregnancy, this additional requirement is approximately 67 $\mu\text{g/day}$ of absorbed copper or 100 $\mu\text{g/day}$ of dietary copper, a value based on 65 to 70 percent bioavailability and rounding. Evidence suggests that copper absorption may be more efficient during pregnancy, and such efficiency could result in absorption of this amount of copper (Turnlund et al., 1983); therefore no additional increment would be required. However, too few data are available to draw this conclusion. Consequently, an additional 100 $\mu\text{g/day}$ was added to the EARs for adolescent girls and women during pregnancy for EARs of 785 and 800 $\mu\text{g/day}$, respectively.

Copper EAR and RDA Summary, Pregnancy

EAR for Pregnancy

14–18 years	785 µg/day of copper
19–30 years	800 µg/day of copper
31–50 years	800 µg/day of copper

The data available to set an EAR are limited for men and women, as well as the number of levels of dietary copper in the depletion/repletion studies. Thus, a CV of 15 percent is used because information is not available on the standard deviation of the requirement for pregnant women. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of individuals in the group (therefore, for copper the RDA is 130 percent of the EAR). The calculated RDA is rounded to the nearest 100 µg.

RDA for Pregnancy

14–18 years	1,000 µg/day of copper
19–30 years	1,000 µg/day of copper
31–50 years	1,000 µg/day of copper

Lactation

Evidence Considered in Estimating the Average Requirement

The EAR for lactation is determined on the basis of the copper intake necessary to replace copper secreted daily in human milk plus the EAR for adolescent girls and adult women. The average amount of copper that is secreted in human milk and must be absorbed is approximately 200 µg/day. Copper bioavailability for the adult consuming the EAR for copper is about 65 to 70 percent; therefore an additional 300 µg/day of copper must be consumed to replace the copper secreted in human milk, assuming that there is no increase in the efficiency of copper absorption during lactation. Animal data suggest that maternal absorption of copper increases during lactation and could provide for about half of the added increment, but data are not available for humans on copper absorption during lactation.

Copper EAR and RDA Summary, Lactation

EAR for Lactation

14–18 years	985 µg/day of copper
19–30 years	1,000 µg/day of copper
31–50 years	1,000 µg/day of copper

The data available to set an EAR are limited for men and women, as is the number of levels of dietary copper in the depletion/repletion studies. Thus, a CV of 15 percent is used because information is not available on the standard deviation of the requirement for lactating women. The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of individuals in the group (therefore, for copper the RDA is 130 percent of the EAR). The calculated RDA is rounded to the nearest 100 µg.

RDA for Lactation

14–18 years	1,300 µg/day of copper
19–30 years	1,300 µg/day of copper
31–50 years	1,300 µg/day of copper

INTAKE OF COPPER

Food Sources

Copper is widely distributed in foods. The accumulation of copper in plants is not affected by the copper content of the soil in which they grow. Organ meats, seafood, nuts, and seeds are major contributors of dietary copper (Pennington et al., 1995). Wheat bran cereals and whole grain products are also sources of copper. Foods that contribute substantial amounts of copper to the U.S. diet include those high in copper, such as organ meats, grains, and cocoa products, and those relatively low in copper that are consumed in substantial amounts, such as tea, potatoes, milk, and chicken.

Dietary Intake

Data from nationally representative U.S. surveys are available to estimate copper intakes (Appendix Tables C-15, C-16, D-2, E-3). The median intake of copper for women is approximately 1.0 to 1.1 mg/day, whereas the median intake for men ranges from 1.2 to 1.6 mg/day (Appendix Tables C-15 and D-2).

Intake from Supplements

In 1986, approximately 15 percent of adults in the United States consumed supplements that contained copper (Moss et al., 1989; see Table 2-2). Based on data from the Third National Health and Nutrition Examination Survey provided in Appendix Table C-16, the median dietary plus supplemental copper intake was similar to the intake from food alone. The mean intake of dietary and supplemental copper (1.3 to 2.2 mg/day) was approximately 0.3 to 0.5 mg/day greater for men and women than the mean intake from food (1.0 to 1.7 mg/day).

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving copper under medical supervision.

Hazard Identification

Reviews of the toxicity studies in experimental animals (ATSDR, 1990; EPA, 1987; IPCS, 1998; NRC, 1977) indicate that these studies are not useful for setting a UL for humans. Very few of these studies used chronic exposures, only one or two doses were used, and the reporting of experimental details and results was incomplete. In addition, some studies used routes of exposure that are not relevant to human intake (Toyokuni and Sagripanti, 1994). Finally, animal species vary markedly in their sensitivity to copper (Davis and Mertz, 1987); thus it is difficult to determine the most appropriate model in which to assess human toxicity to copper.

The long-term toxicity of copper is not well studied in humans, but it is rare in normal populations not having some hereditary defect in copper homeostasis (Olivares and Uauy, 1996). Copper homeostasis is affected by the interaction among zinc, copper, iron, and molybdenum. In addition, the level of dietary protein, interact-

ing cations, and sulfate all can influence the absorption and utilization of copper (Davis and Mertz, 1987). Therefore, the derivation of a UL for copper must be made in the context of these interactions. The adverse effects associated with intake of soluble copper salts in supplements and drinking water are reviewed below.

Adverse Effects

Gastrointestinal Effects. There are data from studies of humans indicating gastrointestinal illness including abdominal pain, cramps, nausea, diarrhea, and vomiting from the consumption of beverages or drinking water containing high levels of copper (Berg and Lundh, 1981; Knobeloch et al., 1994; Olivares et al., 1998; Pizarro et al., 1999; Spitalny et al., 1984; Wylie, 1957). Many of these studies had serious experimental design weaknesses and involved very few subjects, or the copper exposures were extremely poorly characterized. Thus they are not suitable for the development of a UL.

In a survey of gastrointestinal effects resulting from high levels of copper in carbonated soft drinks, Donohue (1997) reported adverse effects at copper intakes of 4 mg/L. This concentration is equivalent to approximately 4.8 mg/day based on a mean intake of 1.2 L/day of water (Appendix Table C-27). In a double-blind study, 60 healthy Chilean women were given normal drinking water to which graded concentrations of copper sulfate had been added for 11 weeks (Pizarro et al., 1999). Although the exact threshold could not be determined, the authors reported an increased incidence of nausea and other gastrointestinal effects at copper levels greater than 3 mg/L. The mean consumption of water was 1.6 L/day, and therefore the average copper intake from water was 4.8 mg/day. From these two studies it would appear that the threshold for acute gastrointestinal effects from copper in water is about 4.8 mg/day. However, individuals may be able to adapt to even higher concentrations of copper in drinking water. No adverse gastrointestinal effects were reported in U.S. adults who consumed water containing approximately 8.5 to 8.8 mg/L of copper for over 20 years beginning in childhood (aged 0 through 5 years) (Scheinberg and Sternlieb, 1996). Based on water consumption data from the 1988–1994 Third National Health and Nutrition Examination Survey (NHANES III) (Appendix Table C-27), the mean water consumption for young children is approximately 400 mL, which would be equivalent to 3.5 mg/day of copper.

Liver Damage. Liver damage in humans is observed almost exclusively in patients with Wilson's disease and children with Indian childhood cirrhosis (ICC) and idiopathic copper toxicosis (ICT). ICC and ICT have been associated with high copper intakes. However, familial relationships and genetic factors are required for the expression of liver toxicity from high levels of copper intake (Joshi et al., 1987; Kishore and Prasad, 1993; Pandit and Bhawe, 1996; Tanner, 1998). The rarity of ICT and ICC outside of Germany and India and the lack of liver damage noted in children in the United States exposed to levels of copper between 8.5 and 8.8 mg/L in drinking water support the hypothesis that copper is only one factor required for the expression of these diseases (Scheinberg and Sternlieb, 1994).

Further evidence of an underlying hereditary defect in copper homeostasis in ICC comes from Kishore and Prasad (1993). These authors found that one-third of the ICC cases examined have α -1-antitrypsin deficiency. In view of the weight of evidence supporting a genetic basis for the liver damage in Wilson's disease, ICC, and ICT, it is not appropriate to use data from such populations to develop a UL for copper in populations with normal copper homeostatic mechanisms.

Pratt and coworkers (1985) reported no evidence of liver damage or gastrointestinal effects in a double-blind study of seven subjects given 10 mg/day of copper gluconate for a period of 12 weeks. Although from a small study, these results are consistent with the safe upper level of intake of 10 to 12 mg/day of copper proposed by the World Health Organization (WHO, 1996) and the International Programme on Chemical Safety (IPCS, 1998). At higher doses, acute liver failure was reported in one subject, who had no known genetic defect in copper homeostasis, after consuming 30 mg/day of copper from supplements for 2 years, followed by 60 mg/day for an additional but unspecified period of time (O'Donohue et al., 1993).

Other Systemic Effects. Little evidence indicates that chronic exposure to copper results in systemic effects other than liver damage. No association between the level of copper intake and spontaneous abortions has been found, and data are inadequate to assess the reproductive or developmental effects of copper in humans (IPCS, 1998). Also, there is little convincing evidence that copper is causally associated with the development of cancer in humans.

Summary

On the basis of considerations of causality, relevance, and the quality and completeness of the database, liver damage was selected as the critical endpoint on which to base a UL. The selection of gastrointestinal effects as a critical endpoint was considered because of the data involving acute ingestion of soluble (highly ionized) copper salts in drinking water. However, in the United States and Canada, liver damage is a much more relevant endpoint because of the potential for excess intake from food and supplements. Furthermore, extensive evidence from studies in humans and experimental animals indicates that liver damage is the critical endpoint resulting from daily intake of high levels of copper salts (IPCS, 1998).

Dose-Response Assessment

Adults

Data Selection. The human data evaluating liver effects after chronic consumption of copper gluconate appear most relevant to setting a UL. The UL derived below does not apply to individuals at increased risk of adverse effects from excess intake of copper. These subgroups are identified under “Special Considerations.”

Identification of a No-Observed-Adverse-Effect Level (NOAEL) and a Lowest-Observed-Adverse-Effect Level (LOAEL). A NOAEL of 10 mg/day of copper was identified on the basis of the results of Pratt and coworkers (1985). In a 12-week, double-blind study, 10 mg of copper as copper gluconate capsules was consumed daily by seven adults. Liver function tests were normal. From a case report, consumption of 30 mg/day as copper tablets for 2 years, followed by 60 mg/day for an additional period of time, resulted in acute liver failure (O’Donohue et al., 1993).

Uncertainty Assessment. The NOAEL of 10 mg/day was considered to be protective of the general population. Therefore, an uncertainty factor (UF) of 1.0 was selected. A larger UF was considered unnecessary in view of the large international database in humans indicating no adverse effects from daily consumption of 10 to 12 mg/day of copper in foods and the rarity of observed liver damage from copper exposures in human populations with normal copper homeostasis.

Derivation of a UL. The NOAEL of 10 mg/day was divided by the UF of 1.0 to obtain a UL of 10 mg/day (10,000 µg/day) of copper intake from food and supplements.

$$\text{UL} = \frac{\text{NOAEL}}{\text{UF}} = \frac{10 \text{ mg/day}}{1.0} = 10 \text{ mg/day}$$

Copper UL Summary, Ages 19 Years and Older

UL for Adults

≥ 19 years 10 mg/day (10,000 µg/day) of copper

Other Life Stage Groups

Infants. For infants, the UL was judged not determinable because of insufficient data on adverse effects in this age group and concern about the infant's ability to handle excess amounts of copper. To prevent high levels of copper intake, the only source of intake for infants should be food and formula.

Children and Adolescents. In the general, healthy population there are no reports of liver damage from copper ingestion; however, there are many reports of liver damage in children having defects in copper homeostasis. Given the dearth of information, the UL values for children and adolescents are extrapolated from those established for adults. Thus, the adult UL of 10,000 µg/day of copper was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 2 using reference weights from Chapter 1 (Table 1-1). Values have been rounded down.

Pregnancy and Lactation. No studies involving supplemental copper intake by pregnant or lactating women were found. Given the dearth of information, it is recommended that the UL for pregnant and lactating females be the same as that for the nonpregnant and nonlactating females.

Copper UL Summary, Ages 0 through 18 Years, Pregnancy, Lactation

UL for Infants

**0–12 months Not possible to establish; source of intake
should be from food and formula only**

UL for Children

1–3 years	1 mg/day (1,000 µg/day) of copper
4–8 years	3 mg/day (3,000 µg/day) of copper
9–13 years	5 mg/day (5,000 µg/day) of copper

UL for Adolescents

14–18 years	8 mg/day (8,000 µg/day) of copper
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UL for Pregnancy

14–18 years	8 mg/day (8,000 µg/day) of copper
19–50 years	10 mg/day (10,000 µg/day) of copper

UL for Lactation

14–18 years	8 mg/day (8,000 µg/day) of copper
19–50 years	10 mg/day (10,000 µg/day) of copper

Special Considerations

Certain subgroups may be at increased risk of adverse effects from excess intake of copper (Joshi et al., 1987; Kishore and Prasad, 1993; Pandit and Bhawe, 1996; Scheinberg and Sternlieb, 1996; Tanner, 1998). These include individuals with Wilson's disease (homozygous), ICT, and ICC. In addition, heterozygotes for Wilson's disease may be at increased risk of adverse effects from excess copper intake.

Intake Assessment

Based on data from NHANES III (Appendix Table C-16), the highest median intake of copper from the diet and supplements for any gender and life stage group was about 1,700 µg/day for men aged 19 through 50 years and about 1,900 µg/day for lactating women. The highest reported intake from food and supplements at the ninety-ninth percentile was 4,700 µg/day in lactating women. The next highest reported intake at the ninety-ninth percentile was 4,600 µg/day in pregnant women and men aged 51 through 70 years.

In situations where drinking water that contains copper at the present U.S. Environmental Protection Agency (EPA) Maximum Contaminant Level Goal is consumed daily, an additional intake of 2,600 µg of copper in adults and 1,000 µg in 1- through 4-year-old children is possible. However, as reported by IPCS (1998), data from the EPA indicate 98 percent of flushed drinking water samples had copper levels of less than 460 µg/L. According to these values, most

of the U.S. population receives less than 100 to 900 $\mu\text{g}/\text{day}$ of copper from drinking water.

Whether total daily intakes of copper will lead to adverse health effects will depend upon the species of copper in the media of concern, its degree of ionization, and its bioavailability.

Risk Characterization

The risk of adverse effects resulting from excess intake of copper from food, water, and supplements appears to be very low in adults at the highest intakes noted above. However, copper intake data indicate that a small percentage of children aged 1 through 8 years are likely to exceed the UL for their age group. Although members of the general population should be advised not to exceed the UL routinely, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving copper under medical supervision.

RESEARCH RECOMMENDATIONS FOR COPPER

- Determine the specific health risks associated with marginal copper deficiency.
- Define the adverse effects of chronic high copper consumption for establishing upper intake levels and to evaluate the health effects of copper supplements.
- Determine the involvement of low and high copper intakes on neurological and cognitive function.

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