Copper[1,2]

Copper is the 26th element in abundance in the crust of the earth and is the 29th element in the periodic table with 2 stable and 9 radioactive isotopes. Copper deficiency is the leading deficiency worldwide among nutritional diseases of agricultural animals. The essentiality of copper for animals and humans has been known for nearly a century. Needed in only trace amounts, the human body contains slightly >100 mg, although measurements are scarce. Only kidney and liver exceed the concentration of copper in brain (~5 μg/g), with heart being close behind. These high concentrations are probably related to metabolic activity, because copper is a cofactor for cytochrome c oxidase, the terminal enzyme in the electron transport chain. Because of their size, skeleton and muscle contain more than one-half of the copper in the body.

Deficiencies: Adequate copper intake permits normal utilization of dietary iron in that intestinal iron absorption, iron release from stores (e.g. in macrophages of liver and spleen), and iron incorporation into hemoglobin are copper-dependent processes. In addition to preventing anemia, copper assists in blood coagulation and blood pressure control; cross-linking of connective tissues in arteries, bones, and heart; defense against oxidative damage; energy transformation; myelination of brain and spinal cord; reproduction; and synthesis of hormones. Inadequate copper produces adverse effects on the metabolism of cholesterol and glucose, blood pressure control and heart function, mineralization of bones, and immunity. Isoprostanes are also known to increase during copper deficiency (1). Moreover, it is now an accepted medical fact that copper-deficient humans also suffer from osteoporosis, which can be cured with extra copper. Although it is unknown whether copper deficiency contributes to osteoporosis in Western populations, 2 double-blind, placebo-controlled trials have shown that trace element supplements, including copper, improved bone mineral density in postmenopausal women (1). Further, as much as 1.03 mg copper/d has been proven insufficient for adult males (2).

Diet recommendations: Dietary reference intakes for copper were established almost a decade ago (3). Based on a lack of experimental data, Adequate Intake levels for copper have been established for infants 0–6 mo of age (200 μg/d) and for those between 7 and 12 mo (220 μg/d). The RDA increases throughout childhood and adolescence (all in μg/d: 1–3 y old, 340; 4–8 y, 440; 9–13 y, 700; 19–50+ y, 900). Copper needs increase in pregnancy (1000 μg/d) and lactation (1300 μg/d). Upper tolerable intake levels have also been established for copper, varying from 1000 μg/d at 1–3 y old to 10,000 μg/d in adults. Interestingly, copper recommendations for adults in the UK, the European Community, and Australia/New Zealand range from 1.1 to 1.2 mg/d, suggesting that the U.S. and Canadian RDA values for adults may be low.

The relative amount of copper in the diet seems to be the major predictor of intestinal absorption, although percent absorption increases during states of deficiency. Dietary factors, including iron, vitamin C, and zinc, have been reported to exert adverse effects on the bioavailability of copper. Lead poisoning, hemochromatosis, and excessive ingestion of soft drinks produce more subtle effects. Bariatric surgery and excessive use of denture creams high in zinc are the most recently identified ways of inducing deficiency (1). The impact of dietary components on copper absorption may be more pronounced in neonates, as digestive function and homeostatic regulation of biliary copper excretion are immature.

Deficiency occurs when requirements exceed intakes; little is known about the variability of adult copper requirements. Recent reviews of deficiency (4–6) reveal that 20–40% of cases are of unknown origin. Whether these individuals have low intakes or unusually high requirements is unknown.

Food sources: Copper absorption, at 55–75%, is considerably higher than for that of other trace elements; absorption occurs mainly in the upper small intestine. The copper concentration of foods is an important characteristic determining nutritional usefulness. In order of increasing concentration on a weight basis, fats and oils, dairy products, sugar, tuna, and lettuce are low in copper (all <0.4 μg/g); legumes, mushrooms, chocolate, nuts and seeds, and liver are high in copper (all >2.4 μg/g). Although not high in copper, bread, potatoes, and tomatoes are consumed

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in sufficiently large amounts by U.S. adults to substantially contribute to copper intake. Copper and magnesium are highly correlated in U.S. diets and food groups high in folate tend to be high in copper (1).

Clinical uses: Copper gluconate is the only copper supplement listed by the United States Pharmacopeial Convention for oral use. A recent study supplemented adults with 10 mg cupric gluconate/d for 12 wk without evidence of liver damage or gastrointestinal distress (7). Cupric oxide is contained in some vitamin-mineral supplements but is poorly utilized. Deficient people should be supplemented with several times the EAR or RDA, because these recommendations are only for healthy people. Adults have tolerated daily supplements of 3–7 mg for long periods (1).

No single indicator provides an adequate assessment of copper nutriture. Reductions in plasma copper and ceruloplasmin (CP) activity are noted in severely copper-deficient humans; CP carries the predominance of copper in the blood, so alterations in blood copper likely reflect the amount of circulating CP. Observed reductions in serum Cu and CP activity are, however, complicated by the fact that several physiological alterations can increase copper content and CP activity in blood, including the acute phase response to infection and inflammation, pregnancy and other hormonal perturbations, some carcinogenic phenotypes, and smoking. Circulating copper may thus be unexpectedly high during inflammation and may not reflect the actions of copper-dependent enzymes in cells. Furthermore, numerous experiments with animals reveal that plasma copper can be normal or increased even though copper in liver and other organs is low. Low plasma copper indicates physiological impairment (1). Better indices, particularly for the detection of moderate deficiency, are clearly needed (8–10).

Toxicity: Copper toxicity is rather rare in humans and animals, because mammals have evolved precise homeostatic control of copper due to the high reactivity of the free metal. Free copper in cells and in the body is extremely low; copper almost always exists in biological systems bound to proteins. Ingestion of high copper levels may, however, override the innate checkpoints designed to regulate overall body copper levels, including, but not limited to, enhanced intestinal absorption in the absence of a physiological demand for copper. Due to possible adverse consequences of high copper ingestion, an upper tolerable intake level of 10 mg/d has been established (3). Copper toxicity risks are higher for neonates and infants given an immature biliary excretion system and enhanced intestinal absorption. Copper loading is observed clinically today in the setting of Wilson's disease and other disorders in which biliary copper excretion is impaired, such as biliary cirrhosis and biliary atresia.

Recent research: Traditional approaches to copper nutrition have emphasized either anemia or the nutrition of infants. Descriptions of anemia with hypochromic, microcytic erythrocytes can be found in many textbooks.

Two new adult syndromes are being identified along with the new ways of becoming deficient (above). Leukocytes also can be affected by deficiency; some cases of myelodysplastic syndrome respond to copper supplementation (1).

Neuromuscular defects resembling those of pernicious anemia and responding to copper instead of vitamin B_{12} are being increasingly reported and have been referred to as "human swayback" in reference to well-known copper deficiency in ruminants (4–6,11). The similarity of these syndromes might not be as mysterious as it may seem. Nitrous oxide anesthesia can induce vitamin B_{12} deficiency very rapidly by inactivating methionine synthase (12), which requires vitamin B_{12} for activity (13). Activity of this enzyme is decreased in copper-deficient rats, suggesting it may be a copper enzyme (14).

An extensive body of recent literature has explored the interaction between copper and iron (15); certain aspects of these interactions have in fact been recognized for $>$150 y (16). Described points of interaction include 2 multicopper ferroxidases, which are important for intestinal copper absorption (hephaestin) and release of iron from body stores (CP). The expression and activity of both ferroxidases is decreased in copper-deficient rodents. Moreover, CP expression and activity increases during iron deficiency anemia in humans (17) and rodents (18), suggesting that it may play a compensatory role in the response to low body iron levels. Further studies have revealed alterations in the expression of copper homeostasis-related genes in the intestines of iron-deficient rodents, including the Menkes copper ATPase (Atp7a, a copper exporter)

and metallothionein, an intracellular copper storage protein, again suggesting that copper is important for the proper response to decreased body iron stores (19,20).

Additional Information: IOM. Dietary reference intakes. The essential guide to nutrient requirements. Otten JJ, Hellwig JP, Meyers LD, editors. Washington, DC: The National Academies Press; 2006. p. 5–17, 305–11.

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