

Copper

Function

The essential role of copper was recognized after animals that were fed only a whole-milk diet developed an apparent deficiency that did not respond to iron supplementation (Turnlund 1999). The similarities between copper-deficiency anemia and iron deficiency helped scientists to understand copper's important biological role as the activator of the enzyme ferroxidase I (ceruloplasmin), which is necessary for iron absorption and mobilization from storage in the liver (Turnlund 1999; Linder 1996). Copper activates several enzymes involved in the metabolism of amino acids and their metabolites, energy, and the activated form of oxygen, superoxide. Enzyme activation by copper produces physiologically important effects on connective tissue formation, iron metabolism, central nervous system activity, melanin pigment formation, and protection against oxidative stress.

There are two known inborn errors of copper metabolism: Wilson's disease, which results when an inability to excrete copper causes the element to accumulate, and Menkes' disease, which results when an inability to absorb copper creates a copper deficiency (Turnlund 1999).

Safety Evidence

Copper is relatively nontoxic in most mammals, including humans (Scheinberg and Sternlieb 1976; Linder 1996). Excess copper intake that causes acute or chronic adverse effects is rare. Nevertheless, the adverse effects that may occur after acute intake of massive amounts of copper include epigastric pain, nausea, vomiting, and diarrhea (Turnlund 1999; Food and Nutrition Board 2001). These reactions tend to eliminate the large amounts of ingested copper that caused them, and thereby help reduce the risk of their more serious manifestations, which can include coma, liver and kidney pathologies, and death. Adverse effects related to longer-term ingestion of excess copper have been reported for infants in India. These cases of "Indian childhood cirrhosis" arose after milk formula was heated in brass pots, which leached large amounts of copper into the formula (Linder 1996). The intakes of copper associated with these cases are not known. Similar effects can be produced in animals by feeding them diets that contain very large amounts of copper (e.g., 2,000 mg per kg of feed).

Published Official Reviews of Copper Safety

The FNB reviewed the evidence related to possible adverse effects of copper on the gastrointestinal tract, liver, and other systems (Food and Nutrition Board 2001). Using data from the clinical trial of Pratt and coworkers, which showed no liver toxicity, FNB identified a NOAEL of 10 mg per day as supplemented copper gluconate (Pratt et al. 1985). The UF of 1.0, based on a large international database indicating no adverse effects associated with copper intake of 10 to 12 mg per day, was selected to derive an FNB UL of 10 mg per day. This UL nominally applies to total intake from all sources, but it was derived from data on supplemental use of 10 mg per day in persons with unspecified dietary copper intake. The FNB identified 1.2 to 1.6 mg per day as a typical copper intake from foods. Its report states clearly that the UL does not apply to persons with Wilson's disease or any other disorders that cause copper retention and toxicity.

The EC SCF reviewed the evidence related to acute and chronic toxicities caused by excess copper intake (Scientific Committee on Food 2003). For chronic toxicity, the following possible toxicities were considered: carcinogenicity, genotoxicity, increased risk of coronary heart disease, and neurological disease. The EC SCF also identified a NOAEL of 10 mg per day, based on the same evidence (Pratt et al. 1985) also selected by FNB. Keeping in mind that the body burden of copper increases at different intake levels, EC SCF selected a UF of 2 to derive a UL of 5 mg per day. It was noted that the 97.5 percentile of copper intake in Europe approaches the UL for adults (i.e., less than 5 mg per day), a matter that was not considered to be of concern.

The UK EVM reviewed the same human evidence relied upon by FNB and EC SCF, but elected to derive an SUL from animal studies (Expert Group on Vitamins and Minerals 2003). Looking at data obtained from a wide range of copper intakes (Herbert et al. 1993), UK EVM identified a NOAEL for copper (as copper sulfate) of 16 mg per kg body weight in male rats. From this NOAEL value, EVM derived an SUL of 10 mg per day by using a composite UF of 100 and correcting to a 60 kg human body weight. This SUL is intended to apply to total intake from all sources. The UK EVM expressed concern that copper intakes from water may reach 6 mg per day in some groups in the UK.

CRN ULS for Copper

The NOAEL of 10 mg per day identified by FNB and EC SCF was derived from a clinical trial of supplemental copper in subjects with unspecified dietary copper intake. CRN concludes that this value represents the supplemental copper NOAEL from current data. Considering the absence of adverse effects at intakes

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in the range of 10 to 12 mg per day, and the fact that the usual intake of copper is
less than 2 mg, CRN identifies 9 mg as the ULS for supplemental copper.

<u>Comparison of Safety Values for Copper</u>	
CRN ULS	9 mg
US FNB UL	10 mg
EC SCF UL	5 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL	10 mg

References

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