

Copper

Introduction

Copper, like iron and some other elements, is a transition metal and performs at least some of its functions through oxidation-reduction reactions. These reactions involve the transition from Cu^{1+} to Cu^{2+} . There is little or no Cu valence 0 (the metallic form) in biological systems (European Commission, Scientific Committee on Food [EC SCF] 2003).

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 and was then recognized as a copper deficiency (Turnlund 1999). The similarity of copper-deficiency anemia and iron-deficiency anemia 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 (Linder 1996; Turnlund 1999; EC SCF 2003). 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 disease results when an inability to excrete copper causes the element to accumulate, and Menkes disease results when an inability to absorb copper creates a copper deficiency (Turnlund 1994).

Safety Considerations

Copper is relatively nontoxic in most mammals, including humans (Scheinberg and Sternlieb 1976; Linder 1996). Excess copper intakes that cause acute or chronic adverse effects are rare, as absorption is decreased and excretion is increased to maintain homeostasis in response to large amounts of copper. Because of species and dietary differences (e.g., variations in iron, zinc, and

molybdenum in the diet), the minimum toxic copper level varies. Additionally, the chemical form of copper has an impact on susceptibility to copper toxicity (EC SCF 2003).

The adverse effects that may occur after acute intake of massive amounts of copper include epigastric pain, nausea, vomiting, and diarrhea (Turnlund 1999; Institute of Medicine [IOM] 2001). These reactions tend to eliminate the large amounts of ingested copper that caused them and thereby help reduce the risk of its 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). In humans, chronic copper toxicity has its most pronounced effects on liver function (EC SCF 2003).

Official Reviews

IOM (2001). The IOM reviewed the evidence related to possible adverse effects of copper on the gastrointestinal tract, liver, and other systems. Using data from the clinical trial of Pratt and coworkers, which showed no liver toxicity, the IOM 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 intakes of 10 to 12 mg per day, was selected to derive an IOM UL of 10 mg per day. This UL nominally applies to total intakes from all sources, but it was derived from data on supplemental uses of 10 mg per day in persons with unspecified dietary copper intakes. The IOM 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 disease or any other disorders that cause copper retention and toxicity.

EC SCF (2003). The EC SCF, in preparing its opinion on the tolerable upper intake level of copper, reviewed the evidence related to acute and chronic toxicities caused by excess copper intake. 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) selected by the IOM. Keeping in mind that the body burden of copper increases at different intake levels, the 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.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM reviewed the same human evidence relied upon by the IOM and EC SCF, but elected to derive an SUL from animal studies. Looking at data obtained from a wide range of copper intakes (Herbert et al. 1993), the EVM identified a NOAEL for copper (as copper sulfate) of 16 mg per kg of body weight in male rats. From this NOAEL value, the 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 intakes from all sources. The EVM expressed concern that copper intakes from water may reach 6 mg per day in some groups in the United Kingdom.

CRN Recommendations

The NOAEL of 10 mg per day identified by the IOM and the 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 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 UL for supplemental copper.

Quantitative Summary for Copper

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| CRN UL, supplemental intake | 9 mg/day |
| IOM UL, total intake | 10 mg/day |
| EC SCF UL, total intake | 5 mg/day |
| EC supplement maximum | Not determined |
| EVM SUL, total intake | 10 mg/day |

References

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