Copper

Copper		Adults	Children		
	mg/d		2-5 y	6-9 y	10-13 y
Recommended intake	RI	0.9	0.4	0.5	0.7
Average requirement	AR	0.7			
Lower intake level	LI	0.4			
Upper intake level	UL	5.0			

Introduction

Copper has two oxidation states and is involved in oxidation and reduction processes inside cells. Copper functions as a component of a number of enzymes involved in energy metabolism, formation of connective tissue and defence against free radicals.

Dietary sources and intake

Copper is widely distributed in food. The highest levels of copper are found in liver and other offal, while milk and milk products have a low copper content. Most grain products, meats, chocolate products, dried fruits, mushrooms, tomatoes, banana and potatoes contain intermediate amounts. The intake of copper in the Nordic countries varies between 1.0 and 2.0 mg/d [1].

Physiology and metabolism

Copper absorption occurs primarily in the small intestine. At normal dietary intakes (1-5 mg/day) absorption varies between 35 and 70 % and is mainly regulated by the amount of copper in the diet. In the enterocyte copper is bound to a copper chaperone or chelated by metallothionein, a protein that is induced by zinc. At high zinc intakes (>50 mg/d), copper absorption is therefore inhibited. The copper chaperones deliver copper to copper transporting proteins for the final absorption into circulation. At high levels of dietary copper, passive diffusion also plays a role [2]. After absorption from the gut, copper is transported to the liver bound to albumin, transcuprein, low molecular-weight copper histidine complexes or a combination of these. Once absorbed into the liver it has been suggested that copper is bound to either metallothionein or reduced glutathione, which thereby serves as intracellular copper stores. Turn-over of copper from reduced glutathione or metallothionein makes copper available for other purposes and is transported by chaperones. For example, the copper chaperone CCS1 guides copper to superoxide dismutase [3]. Homeostasis of copper is

regulated to some extent by absorption, but also through excretion via bile and approximately 0.5 to 1.5 mg copper/d is excreted through the intestinal tract in this way. Urinary excretion of copper is low.

The total body content of copper for an adult is approximately 50 to 120 mg: 40 % is contained in muscle tissue, 15 % in liver, 10 % in brain, and approximately 6 % in plasma and erythrocytes. Newborn infants have a higher content of copper in the liver than adults, and this might act as a store of copper during the first couple of months. Copper deficiency in humans is rare, but has been found in a number of circumstances. Copper deficiency has been observed in premature infants fed milk formula, in infants recovering from malnutrition associated with chronic diarrhoea and fed cow's milk [4], and in patients with prolonged total parenteral nutrition without additional copper. Symptoms of copper deficiency in children are low concentrations of white blood cells, anaemia, and hair and skin depigmentation [5]. Heart and skeletal abnormalities have also been observed. Most of the symptoms can be related to the copper-containing enzymes.

There is substantial evidence from animal studies to suggest that diets low in copper reduce the activity of many of the copper-dependent metalloenzymes. The activity of some of these metalloenzymes has also been shown to decrease during human copper depletion [6, 7]. There is also evidence that immune and cardiac dysfunction can occur during experimental copper deficiency and the development of such signs of deficiency has been demonstrated in infants [6, 8]. Furthermore, it has recently been demonstrated that low copper (< 0.6 mg/day compared to >1.5 mg/d) intake might be associated with increased risk of colorectal cancer, as low dietary copper increases fecal free radical production, fecal water alkaline phosphatase activity and cytotoxicity in healthy males [9].

Serum copper and caeruloplasmin concentration are currently used as biochemical indices of copper status and may be used to detect severe copper deficiency.The decline in serum copper and caeruloplasmin concentrations observed when healthy young men were fed a diet containing 0.38 mg/d of copper for 42 days was reversed by copper supplementation [10]. In a number of other studies with higher levels of copper intake, (0.66 mg/d and above), serum copper and caeruloplasmin concentrations did not decline significantly [11, 12], suggesting sufficient intake.

The dietary copper intake at which caeruloplasmin concentration no longer increases in response to increased dietary copper might be considered the copper requirement for caeruloplasmin synthesis. Other suggested indices of copper status include superoxide dismutase activity, platelet copper concentration and cytochrome C oxidase activity,all of which have been shown to decline at low copper intakes. However, none of these have been found suitable for detection of marginal copper deficiency or marginal copper toxicity [13]. Instead, the recently identified Cu chaperone, CCS has been suggested as a potential biomarker for marginal copper deficiency and toxicity [13-15].

Requirement and recommended intake

Adults

The precise requirement for copper is not known. Indications of deficient copper status, using superoxide dismutase (SOD) activity as a marker of Cu status, have been reported with intakes of 0.7 to 1 mg/d [16-18]. However, other studies with less extreme intervention diets have not found indications of changes in copper status; SOD, caeruloplasmin or plasma Cu at intakes of 0.79 mg/d for 42 days [12]. In a subsequent study, an intake of 0.66 mg/d for 24 days followed by an intake of 0.38 mg/d for 42 days resulted in decreasing indicators of copper status with time in young men [10, 19]. Although the levels did not fall into the deficient range, a steady state was not completely reached. Other studies have shown that intakes below 0.7 mg/d are associated with increases in biomarkers related to disease, e.g fecal free radical production, fecal water alkaline phosphatase and cytotoxicity [9] or immunefunction [20]. There are thus limited data to establish an average requirement for copper for adults, but the available data indicate that an intake of approximately. 0.7-0.8 mg/d will maintain adequate copper status, i.e. plasma copper, caeruloplasmin and SOD. The US Food and Nutrition Board base their recommended copper intake for adults on a number of indicators including plasma and platelet copper concentration, serum ceruloplasmin concentration and erythrocyte SOD in controlled depletion-repletion studies [21]. Data on obligatory copper losses were also used. Based on these indicators an average requirement was estimated to be 0.7 mg /d for adults. With a coefficient of variation of 15 %, the RDA was calculated to be 0.9 mg /d. This approach is also adopted in NNR.

Children

The copper content of human milk is highest during early lactation and then declines during the course of lactation. The mean copper content of human milk during the first 6 months of lactation is approximately 0.25 mg/L [22-24]. There are no indications of inadequate copper status in breast-fed infants. For infants 6-11 months the requirements are based on extrapolation from adults with allowance for growth.

The copper requirements for children more than one year old have been calculated from estimates of adult requirement with allowance for growth [21].

Pregnancy and lactation

The extra requirement for copper in pregnancy is relatively low, approximately 0.15 mg/d in the last trimester, and is probably met by adaptation through increased fractional absorption.

The copper content of human milk is approximately 0.22 mg/L. With a milk production of approximately 750 ml/d and an estimated 50 % absorption, an extra 0.3 mg/d during lactation is recommended.

Upper intake levels and toxicity

Intake of high doses of copper leads to acute toxicity, which produces symptoms of gastric pain, nausea, vomiting and diarrhoea. Storage of food in non-galvanised copper containers is

associated with the risk of childhood sclerosis [25]. In areas with soft water, copper can leach from copper tubes and result in high copper concentrations (more than 100 mg/L) in drinking water. Gastro-intestinal disturbances have been seen with intakes of copper-contaminated water containing 3.7 mg/L [26]. Infants are probably the most sensitive group and case studies have indicated an association with intake of copper. Recent controlled and population-based studies found weak evidence for a role of copper from drinking water at concentrations up to 2 mg/L [27]. However, it is considered prudent to recommend letting water run before it is used for consumption by that age group, especially when used for formula.

The Scientific Committee on Food has proposed an upper limit of 5 mg/day to be safe for adults [1]. This is based on the absence of negative effects during copper supplementation and includes a safety factor.

Reasoning behind the recommendation

The recommendations from NNR 2004 are maintained.

There are limited data to establish an average requirement for copper for adults, but the available data indicate that an intake of approximately. 0.7-0.8 mg/d will maintain adequate copper status. With a coefficient of variation of 15 %, the RI was calculated to be 0.9 mg /d.

The copper content of human milk is approximately 0.22 mg/L. With a milk production of approximately 750 ml/d and an estimated 50 % absorption, an extra 0.3 mg/d during lactation is recommended.

The copper requirements for children more than one year old have been calculated from estimates of adult requirement with allowance for growth

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