

## **Zinc**

---

### *Function*

Zinc deficiency can lead to a variety of physiological and developmental impairments. Conditioned zinc deficiency has caused endemic hypogonadism and dwarfism in rural Iran (King and Keen 1999; Cousins 1996). The conversion of the food forms of folic acid (pteroylpolyglutamates) to free folic acid (pteroylmonoglutamate) to permit utilization of food folates is performed by a zinc-dependent enzyme. Zinc is essential for the function of numerous enzymes, including many involved in acid-base balance, amino acid metabolism, protein synthesis, and nucleic acid synthesis and function. The conversion of pteroylheptaglutamate to free folic acid is impaired in men with zinc deficiency. Experimental zinc deficiency leads to reproductive failure and loss of epidermal integrity. Recent studies have shown that zinc is involved in the immune system and necessary for the development and functioning of the nervous system.

Certain chemical similarities cause zinc and copper to interact extensively (King and Keen 1999). Large quantities of zinc can interfere with copper uptake and modify copper binding, and this effect has been used in treating Wilson's disease, a defect that leads to excessive copper storage. Iron can interfere with zinc absorption when the zinc is administered as a solution, but such interference has not manifested itself when zinc is consumed as part of a meal. Although high levels of calcium can also interfere with zinc absorption, the effect has no demonstrated practical importance.

### **Safety Evidence**

Certain folic acid-zinc interactions are well documented (Butterworth and Tamura 1989), but the crucial issue is whether higher intakes of either zinc or folic acid may disrupt the bioavailability or function of the other and, if so, what intakes are associated with such effects. Some reports of zinc-folic acid interactions suggest the possibility that supplemental folic acid could adversely affect zinc nutriture (Mukherjee et al. 1984; Milne et al. 1984; Simmer et al. 1987), but more recent reports have not uncovered any such interaction (Tamura et al. 1992; Kauwell et al. 1995). There are no Medline reports of high zinc intake causing adverse effects through an antagonism of folic acid. Reports of anemia related to excess zinc intake all describe the microcytic, hypochromic anemia associated with copper deficiency, a condition that could also interfere with iron utilization (Greger 1994; Summerfield et al. 1992; Gyorffy and Chan 1992; Frambach and Bendel 1991). All anemia cases that have been associated with zinc involve intakes of more than 110 mg per day.

Zinc supplements of 150 mg per day may also suppress lymphocyte stimulation response, thereby compromising immune function (Chandra 1984; Greger 1994). Supplements of 50 mg or more per day decreased serum HDL cholesterol levels (Freeland-Graves et al. 1982). Total intakes of 60 mg increased levels of copper (Fischer et al. 1984) and iron (Yadrick et al. 1989) and also decreased HDL cholesterol levels (Hooper et al. 1980; Black et al. 1988; Chandra 1984).

## **Published Official Reviews of Zinc Safety**

The FNB found the adverse effects of excess zinc to include a suppressed immune response, decreased HDL cholesterol levels, and a reduced copper status (Food and Nutrition Board 2001). The speculated adverse effects of excess zinc on human reproduction were considered unsupported by convincing evidence. Of the various effects, FNB selected the reduced copper status as the critical effect for deriving a UL for zinc. Specifically, FNB used the data showing suppression of copper-dependent superoxide dismutase at 50 mg of zinc supplementation (Yadrick et al. 1989) to identify a LOAEL. Although no zinc intake from food was identified by Yadrick and coworkers, FNB used population data to estimate a dietary zinc intake of 10 mg for the study. Thus, FNB identified a LOAEL of 60 mg per day for total intake from all sources. A UF of only 1.5 was selected to correct for uncertainty in extrapolation from a LOAEL to a NOAEL, but this value was judged to be adequate because reduced copper status is rare. Thus, the FNB UL for zinc is 40 mg per day for total intake from all sources.

The EC SCF identified a NOAEL for zinc of approximately 50 mg per day (Scientific Committee on Food 2003). This NOAEL represents an overall conclusion based upon several studies. Although zinc intakes of as low as 18.2 mg may decrease copper retention (Festa et al. 1985), this effect is readily corrected by adequate copper intake. Recent balance studies (Davis et al. 2000; Milne et al. 2001) indicate that copper balance and other indicators of copper status can be maintained when zinc intake is as high as 53 mg. No adverse effects were observed with 30 mg of supplemental zinc when dietary zinc was near 10 mg (Bonham et al. 2003a, 2003b). From these data collectively, EC SCF identified a NOAEL of 50 mg of zinc and judged a UF of 2 to be appropriate in deriving a UL of 25 mg for total intake from all sources.

The UK EVM selected a LOAEL of 50 mg (Expert Group on Vitamins and Minerals 2003) for supplemental zinc based on several studies (Yadrick et al. 1989; Black et al. 1988, Cunningham et al. 1994; Davis et al. 2000). To extrapolate from a LOAEL to a NOAEL, UK EVM selected a UF of 2, resulting in a derived SUL of 25 mg for supplemental zinc.

The EPA considers the depressing effect of 60 mg of zinc intake on the copper-dependent form of the enzyme superoxide dismutase (E-SOD) (Yadrick et al.

From: **Vitamin and Mineral Safety 2<sup>nd</sup> Edition** ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

1989) to be the most appropriate basis for a zinc RfD (Cantilli et al. 1994). The RfD method, however, requires selection of a default value of 1, 3, or 10 for each of 5 components of the composite UF, and the resulting RfD (Environmental Protection Agency 2004) is equivalent to 21 mg per day for a 70 kg person.

## **CRN ULS for Zinc**

---

There are no known adverse effects of zinc at chronic supplemental levels of 30 mg per day (Bonham et al. 2003a, 2003b), and this level provides a substantial margin of safety below the levels associated with adverse effects (at least 50 mg of supplemental zinc). Therefore, 30 mg per day is identified as the CRN ULS. Assuming a dietary zinc intake of 10 mg, the CRN ULS is exactly compatible with the 40 mg FNB UL for total intake. The CRN value is only slightly higher than the 25 mg supplemental SUL set by UK EVM.

### **Comparison of Safety Values for Zinc**

<b>CRN ULS</b>	30 mg
<b>US FNB UL</b>	40 mg
<b>EC SCF UL</b>	25 mg
<b>EC supplement maximum</b>	Not established (as of May 2004)
<b>UK EVM SUL, supplement</b>	25 mg

## *References*

Black MR, Medeiros DM, Brunett E, Welke R. Zinc supplementation and serum lipids in adult white males. *Am J Clin Nutr* 1988; 47:970-975.

Bonham M, O'Connor JM, Alexander HD, Coulter SJ, Walsh PM, McAnena LB, Downes CS, Hannigan BM, Strain JJ. Zinc supplementation has no effect on circulating levels of peripheral blood leucocytes and lymphocyte subsets in healthy adult men. *Br J Nutr* 2003a; 89:695-703.

Bonham M, O'Connor JM, Alsh PM, McAnena LB, Downes CS, Hannigan BM, Strain JJ. Zinc supplementation has no effect on lipoprotein metabolism, hemostasis and putative indices of copper status in healthy men. *Biol Trace Elem Res* 2003b; 93:75-86.

Butterworth CE Jr, Tamura T. Folic acid safety and toxicity: A brief review. *Am J Clin Nutr* 1989; 50:353-358.

Cantilli R, Abernathy CO, Donohue JM. In: Mertz W, Abernathy CO, Olin SS, eds. Risk assessment of essential elements. Derivation of the reference dose for zinc. Washington, DC: ILSI Press, 1994; 113-126.

Chandra RK. Excessive intake of zinc impairs immune responses. *JAMA* 1984; 252:1443-1446.

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

Cousins RJ. Zinc. In: Ziegler EE, Filer LJ, eds. Present knowledge of nutrition, 7th ed.  
Washington, DC: ILSI Press, 1996; 293-306.

Cunningham JJ, Fu A, Mearkle PL, Brown RG. Metabolism 1994; 43:558-1562.

Davis CD, Milne DB, Nielsen FH. Changes in dietary copper affect zinc-status indicators of post-  
menopausal women, notable extracellular superoxide dismutase and amyloid precursor proteins.  
Am J Clin Nutr 2000; 71:781-788.

Environmental Protection Agency, 2004. Integrated Risk Information System (IRIS). Zinc and  
Compounds: Reference Dose for Chronic Oral Exposure (RfD). Available online at:  
<http://www.epa.gov/iris/subst/0426.htm>

Expert Group on Vitamins and Minerals. Safe upper levels for vitamins and minerals, Food  
Standards Agency, United Kingdom, 2003.

Festa MD, Anderson HL, Dowdy RP, Ellersiek MR. Am J Clin Nutr 1985; 41:285-292.

Fischer PWF, Giroux A, L'Abbe AR. Effect of zinc supplementation on copper status in adult  
man. Am J Clin Nutr 1984; 40:743-746.

Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron,  
chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.  
Washington, DC: National Academy Press, 2001.

Frambach DA, Bendel RE. Zinc supplementation and anemia [letter]. JAMA 1991; 265:869.

Freeland-Graves JH, Friedman BJ, Han W, Shorey RL, Young R. Effect of zinc supplementation  
on plasma high-density lipoprotein and zinc. Am J Clin Nutr 1982; 35:988-992.

Greger JL. Zinc: Overview from deficiency to toxicity. In: Mertz W, Abernathy CO, Olin SS,  
eds. Risk assessment of essential elements. Washington, DC: ILSI Press, 1994; 91-111.

Gyorffy EJ, Chan H. Copper deficiency and microcytic anemia resulting from prolonged ingestion  
of over-the-counter zinc. Am J Gastroenterol 1992; 87:1054-1055.

Hooper PL, Visconti L, Garry PJ, Johnson GE. Zinc lowers high-density lipoprotein-cholesterol  
levels. JAMA 1980; 244:1960-1961.

Kauwell GP, Bailey LB, Gregory JF III, Bowling DW, Cousins RJ. Zinc status is not adversely  
affected by folic acid supplementation and zinc intake does not impair folate utilization in human  
subjects. J Nutr 1995; 125:66-72.

King JC, Keen CL. Zinc. In: Shils ME, Olson JA, Shike M, Ross CA, eds. Modern nutrition in  
health and disease, 9th ed. Philadelphia: Williams & Wilkins, 1999; 223-339.

Milne DB, Canfield WK, Mahalko JR, Sandstead HH. Effect of oral folic acid supplements on  
zinc, copper, and iron absorption and excretion. Am J Clin Nutr 1984; 39:535-359.

Milne DB, Davis CD, Nielsen FH. Low dietary zinc alters indices of copper function and status in  
postmenopausal women. Nutrition 2001; 17:701-708.

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

Mukherjee MD, Sandstead HH, Ratnaparkhi MV, Johnson LK, Milne DB, Stelling HP. Maternal zinc, iron, folic acid, and protein nutrition and outcome of human pregnancy. *Am J Clin Nutr* 1984; 40:496-507.

Simmer K, James C, Thompson RPH. Are iron-folate supplements harmful? *Am J Clin Nutr* 1987; 45:122-125.

Summerfield AL, Steinberg FU, Gonzalez JG. Morphologic findings in bone marrow precursor cells in zinc-induced copper deficiency anemia. *Am J Clin Pathol* 1992; 97:658-665.

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Zinc. European Commission, SCF/CS/NUT/UPPLEV/62 Final, Brussels, 2003.

Tamura T, Goldenberg RL, Freeberg LE, Cliver SP, Cutter GR, Hoffman HJ. Maternal serum folate and zinc concentrations and their relationships to pregnancy outcome. *Am J Clin Nutr* 1992; 56:365-370.

Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper, and zinc status: Response to supplementation with zinc or zinc and iron in adult females. *Am J Clin Nutr* 1989; 49:145-150.