Manganese

Function

Manganese is an essential trace element because it is an activator of several manganese metalloenzymes, including arginase, pyruvate carboxylase, glutamine synthetase, and one form of superoxide dismutase (SOD). Manganese also is a nonspecific activator of several other enzymes. Deficiency of this element has been induced in several animal species by feeding diets low in manganese. Signs of deficiency in animals include impaired growth, skeletal defects, depressed reproductive functions, ataxia in newborns, and defects in metabolism (Nielsen 1999; Keen and Zidenberg-Cherr 1996). The signs and effects of human deficiency have not been clearly established, but some potential cases in adults have shown depressed growth of hair and nails, failure in normal hair pigmentation, dermatitis, and hypocholesterolemia. Manganese deficiency has been suggested as an underlying factor in the development of joint disease, hip abnormalities, and osteoporosis (Keen and Zidenberg-Cherr 1996).

Because it activates manganese SOD, manganese is necessary for normal antioxidant defenses. However, the practical importance of this effect has not been demonstrated, whether because the data on manganese deficiency are inadequate or because other forms of SOD are also active. In animals, manganese protects heart mitochondrial lipids against peroxidation (Malecki and Greger 1996).

Safety Evidence

Manganese is often considered to be one of the least toxic of the trace elements when consumed orally (Nielsen 1999; Keen et al. 1994; Keen and Zidenberg-Cherr 1996). In animals, excess manganese may inhibit iron absorption and result in iron-deficiency anemia. Additional adverse effects of manganese can include depressed growth, decreased appetite, and altered neurological functions. In contrast to the relatively low toxicity of oral manganese, environmental and workplace manganese exposures (mainly via inhalation) have led to a variety of severe neurological and brain effects—including ataxia, a pseudo Parkinson's disease—and behavioral changes (Keen et al. 1994). When administered to animals by injection, manganese is capable of producing central nervous system toxicity (Ingersoll et al. 1995).

Epidemiological reports from Greece provide some evidence of adverse neurological effects in high-manganese areas (Kondakis et al. 1989; Environmental Protection Agency 2004). The manganese content of well water in a high-manganese area of Greece averaged approximately 2 mg per liter, which

translates to an adult lifetime intake of approximately 3 mg per day. Intakes of manganese from food in the high-manganese area were initially estimated to be 10 to 15 mg per day, but this was later revised to 5 to 6 mg per day (Environmental Protection Agency 2004). These reports suggest that the total intake of manganese in the high-manganese area was either approximately 8 to 9 mg or approximately 13 to 18 mg, depending on which food intake data were used. These discrepancies have led others to conclude that the dietary data were not sufficient to permit reliable estimation of the total oral intake of manganese in these areas (Velazquez and Du 1994; Scientific Committee on Food 2000).

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The FNB concluded from the clinical data of Greger (1999) that 11 mg per day of manganese from food had no adverse effect and set this amount as the NOAEL (Food and Nutrition Board 2001).   The FNB also identified a LOAEL of 15 mg on the basis of potentially adverse effects upon manganese-dependent SOD, as well as other changes (Davis and Greger 1992). With no evidence of toxicity at intakes of less than 11 mg per day, a UF of 1.0 was selected, resulting in an FNB UL for manganese of 11 mg per day. Intakes of manganese by men were given as 3.4 mg from foods and 2.4 mg from supplements.

The EC SCF reviewed manganese toxicity but declined to set a UL, citing "the limitations of the human data and the non-availability of NOAELs for critical endpoints from animal studies" (Scientific Committee on Food 2000).

The UK EVM concluded that chronic exposure to excess manganese caused neurotoxicity in humans and animals, but found the data insufficient to set an SUL (Expert Group on Vitamins and Minerals 2003). Instead, a GL was established based on data which found no adverse effects from 4 mg of manganese in addition to the manganese present in foods (Vieregge et al. 1995). On the basis of this information, UK EVM set a GL of 4 mg for supplemental manganese and 12.2 mg for manganese intake from all sources, given an estimated food intake average of 8.2 mg. Because no adverse effects were seen, no correction for uncertainty was deemed necessary. In estimating a mean intake from food of 4.9 mg and from supplements of 10 mg, UK EVM noted that the high manganese intake from tea likely has little impact due to limitation of the absorption by the tannins present.

The EPA has set an RfD for oral manganese equivalent to 10 mg per day for a 70 kg man based on human data NOAEL of 10 mg (Environmental Protection Agency 2004). Any values that might be selected as LOAEL values are much higher, thus justifying the application of a UF of 1 to the 10 mg per day NOAEL, to derive the RfD of 10 mg per day—an amount calculated to represent a safe oral intake.

CRN ULS for Manganese

Several types of data show that oral manganese intakes of up to 10 mg per day do not cause adverse effects in adults (World Health Organization 1973; Freeland-Graves 1987; Food and Nutrition Board 2001; Velazquez and Du 1994). Epidemiological data related to manganese intake from well water in Greece do not provide any reliable estimate that contradicts this conclusion. The potential great variability of manganese intake from food and water, as well as factors that may limit manganese absorption, makes it difficult to set a ULS for supplemental manganese. The variability in manganese intake from foods would seem to argue for caution on supplemental amounts, but the absence of clinical signs of adverse effects (in contrast to biochemical markers) at intakes of up to 20 mg provides reassurance. Considering the low efficiency of manganese absorption and the absence of any credible reports of adverse effects, it seems reasonable to set a ULS for chronically used supplements at 10 mg per day.

Comparison of Safety Values for Manganese

CRN ULS	10 mg
US FNB UL	11 mg
EC SCF UL	Reviewed but not established (inadequate data)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL	4 mg supplement; 12.2 mg total

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