

Manganese

Introduction

Manganese can exist in a number of oxidation states, of which Mn^{2+} is the predominant form in biological systems (European Commission, Scientific Committee on Food [EC SCF] 2000). Manganese is an essential trace element because it is an activator of several metalloenzymes, including arginase, pyruvate carboxylase, glutamine synthetase, and one form of superoxide dismutase (SOD) (Institute of Medicine [IOM] 2001). 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 (Keen and Zidenberg-Cherr 1996; Nielsen 1999). The signs and effect of human deficiency have not been clearly established, but some potential cases in adults have shown failure in normal hair pigmentation, dermatitis, and hypocholesterolemia (IOM 2001). 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, either 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 Considerations

Manganese is considered to be one of the least toxic of the trace elements when consumed orally (Keen et al. 1994; Keen and Zidenberg-Cherr 1996; Nielsen 1999; EC SCF 2000). This may be

attributed to the homeostatic control of manganese absorption that protects the body from exposure to excess manganese (Department of Health and Human Services [DHHS] 2012). In animals, excess manganese has resulted in neurochemical alterations in the brain as well as neuromotor effects and behavioral changes (EC SCF 2000; DHHS 2012). Neurological effects also have been associated with oral exposure to high manganese levels in humans (EC SCF 2000; IOM 2001; DHHS 2012). 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 can produce central nervous system toxicity (Ingersoll et al. 1995).

Epidemiological reports from Greece provide some evidence of adverse neurological effects in high-manganese areas (Environmental Protection Agency [EPA] 1996; Kondakis et al. 1989). The manganese content of well water in the high-manganese area of Greece averaged approximately 2 mg per liter, which translates to an adult lifetime intake of approximately 3 mg per day. Intake of manganese from food in the high-manganese area was initially estimated to be 10 to 15 mg per day, but this was later revised to 5 to 6 mg per day (EPA 1996). These reports suggest that the total intake of manganese in the high-manganese area was either 8 to 9 mg or 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; EC SCF 2000).

Official Reviews

EPA (1996). The EPA has set a reference dose for oral manganese equivalent to 10 mg per day for a 70-kg person based on human data NOAEL of 10 mg. 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 maximum of 10 mg per day—an amount calculated to represent a safe oral intake.

EC SCF (2000). 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.” Based on neurotoxicity findings and the potential increased susceptibility of some population subgroups, the EC SCF noted that “oral exposure to manganese beyond the normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit.”

IOM (2001). The IOM concluded from the clinical data of Greger (1999) that 11 mg per day of manganese from the consumption of Western-type diets had no adverse effect; they therefore set this amount as the NOAEL. The IOM 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 IOM UL for manganese of 11 mg per day.

Expert Group on Vitamins and Minerals (EVM 2003). The UK’s EVM concluded that chronic exposure to excess manganese caused neurotoxicity in humans and animals but found the data insufficient to set an SUL. Instead, a guidance level was established based on the data of Vieregge and coworkers, 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, the EVM set guidance levels 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, the EVM noted that the high manganese intake from tea likely has little impact due to limitation of the absorption by the tannins present in tea.

CRN Recommendations

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 et al. 1987; Velazquez and Du 1994; IOM 2001). Epidemiological data related to manganese intakes 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 UL 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 suggests that such caution is not needed. Considering the low efficiency of manganese absorption and the absence of any credible reports of adverse effects, CRN sets a UL for chronically used supplements at 10 mg per day.

Quantitative Summary for Manganese

CRN UL, supplemental intake	10 mg/day
IOM UL, total intake	11 mg/day
EC SCF UL, total intake	Not determined
EC supplement maximum	Not determined
EVM, guidance level	4 mg/day supplemental; 12.2 mg/day total intake

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