

Risk Assessment

Manganese

General information

Chemistry

Manganese is an abundant metallic element that can exist in a variety of oxidation states. Mn^{2+} and Mn^{3+} are the most biologically important. Within this risk assessment, the word manganese refers to ionic manganese, except when specific manganese compounds are mentioned.

Natural occurrence

Manganese is present both naturally and as a result of contamination in soils, sediments and water.

Occurrence in food, food supplements and medicines

Manganese is present in foods, particularly green vegetables (2 mg/kg), nuts (14.9 mg/kg), bread (8 mg/kg) and other cereals (6.81 mg/kg). Tea is a rich source of manganese, containing 2.71 mg/kg and is the largest contributor to manganese intake. It is present in several licensed medicines, in combination with other substances, in use for prevention and treatment of nutrient deficiencies and other related conditions. Manganese is also present in a number of multi-vitamin and/or mineral food supplements at levels up to 10 mg.

Other sources of exposure

The level of manganese in drinking water ranges from 0.001 to 0.1 mg/L, but is mostly around 0.01 mg/L. Exposure to manganese may also occur through inhalation of airborne particles by miners, smelters and workers in the manufacture of dry batteries.

Recommended amounts

COMA and the WHO were unable to set a specific recommendation for manganese intake. The EU Scientific Committee for Food (SCF) considered a 'safe and adequate intake' to be 1-10 mg/person/day. The US National Research Council (NRC) specified Estimated Safe and Adequate Daily Dietary Intakes (ESADDIs) of 0.3-1, 1-3 and 2-5 mg/day for infants, children and adults respectively.

Analysis of tissue levels and manganese status

A method for assessing manganese status has not been defined, because of an inconsistent relationship between tissue measures and external exposures. Measurement of manganese-specific superoxide dismutase (MnSOD) activity and the ratio between manganese-specific superoxide dismutase and zinc-copper superoxide dismutase activity has been proposed as a method for assessment, but may be confounded by elevated cytokine levels and disease states which increase MnSOD expression, independent of manganese status.

Brief overview of non-nutritional beneficial effects

There have been claims of a variety of beneficial effects on diabetes, fatigue, memory, dizziness, rheumatoid arthritis, schizophrenia, some cases of epilepsy and the Parkinsonian side effects of phenothiazines.

COMA considered there might be a plausible basis for manganese affecting bone health, but that there is currently insufficient evidence to support dietary recommendations in this respect (COMA, 1998).

Function

Manganese is a component of a number of enzymes and activates a range of others. Glycosyl transferases are specifically activated by manganese.

Deficiency

In humans, manganese deficiency has only been observed under experimental conditions where decreased levels of cholesterol and clotting proteins were measured. Black hair was found to redden, fingernail growth slowed and scaly dermatitis was observed. In animals, manganese deficiency is associated with a variety of symptoms including skeletal malformations, and impaired growth and reproductive function.

Interactions

Manganese and iron compete for absorption sites. Fibre, phytate, calcium, phosphorus and magnesium may also interfere with manganese absorption. It has been suggested that ethanol may enhance manganese toxicity.

Absorption and bioavailability

Absorption takes place in the small intestine via a carrier-mediated mechanism; passive diffusion may also occur. Absorption is generally low but appears to be higher in infants and young animals. Bioavailability of manganese from different food types is variable, but appears to be generally low, due to poor solubility.

Distribution and metabolism

In the portal blood manganese may bind to albumin and α_2 macroglobulin. A small proportion of manganese is oxidised to Mn^{3+} , and enters the systemic circulation, possibly by binding to transferrin. Manganese accumulates in mitochondria-rich tissues such as liver and pancreas. Manganese also accumulates in the brain, particularly in the globus pallidus, striatum and substantia nigra.

Excretion

Manganese is excreted largely in the faeces, mostly as a result of biliary excretion, although some direct secretion also occurs. A small amount of manganese is excreted in the urine.

Toxicity

Human data

Occupational exposure, for example in manganese miners and smelters, to high levels of inhaled manganese has been associated with manganism, a neurotoxic condition similar to Parkinson's disease. Drinking water contaminated with manganese has also been associated with neurological and behavioural effects. There is an association between manganese accumulation and liver disease but this may be due to impaired biliary excretion caused by the liver disease rather than manganese toxicity. Effects on the immune system have been reported.

Supplementation studies

Supplementation trials of human volunteers with 15 or 9 mg manganese/day for 124 days and 'many months' respectively have not reported any adverse effects, but it is unclear whether information on such effects was specifically sought.

Animal data

Manganese has low acute toxicity but neurotoxic effects have been observed in animals chronically fed high concentrations of manganese salts in the diet. High doses of manganese have also resulted in anaemia as a result of iron sequestration. Fertility is reduced by high doses of manganese but other reproductive parameters are unaffected.

Carcinogenicity and genotoxicity

Manganese has been tested in bioassays in rats and mice. No clear evidence of carcinogenicity has been found in either species. Some positive *in vitro* mutagenicity tests have been reported, although results are generally mixed. Studies in mice have indicated that manganese is not mutagenic *in vivo*.

Mechanism of toxicity

Several hypotheses have been proposed to explain the neurotoxicity of manganese, including irreversible oxidation of dopamine, via the reduction of Mn^{3+} to Mn^{2+} or interference with calcium. Other hypotheses include inhibition of mitochondrial respiration, decreased glutathione peroxidase and oxidant damage.

Dose-response characterisation

Manganese is a known neurotoxin at high occupational levels of inhalation exposure. However, it has also been suggested that exposure from lower levels in drinking water may result in more subtle neurological effects in human populations. Neurological effects have been reported at estimated intakes of 3.6-4.6 mg manganese from water, though comparable intakes have been negative in other studies. Other more limited data suggest that adverse effects may occur at even lower intake levels in children. In laboratory animals, adverse effects have been reported following long term exposure to manganese at doses greater than 50-200 mg/kg bw/day. Detailed neurological examinations were performed in only one study in mice which detected effects at ≥ 130 mg/kg bw/day.

Vulnerable groups

Anaemic individuals may be vulnerable to the toxic effects of manganese due to the increased absorption that occurs in states of iron deficiency. Groups with impaired biliary clearance, such as patients with liver disease or older people, may also be susceptible to manganese accumulation and toxicity. It has also been reported that ethanol and long-term use of anti-psychotic drugs increases the susceptibility of humans to manganese toxicity.

Genetic variations

No genetic variations increasing susceptibility to manganese have been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

Kondakis et al., 1989

This was a retrospective study of three cohorts exposed to water containing 0.0036-0.015, 0.08-0.25 or 1.8-2.3 mg/L manganese. The subjects were all aged over 50 years and had been exposed to manganese for >10 years. No estimates of the actual amount of water consumed or the manganese content of the diet were provided, although the 3 cohorts were considered to be comparable. Assuming 2L/day water consumption, intakes for the three groups can be estimated to be 0.0072-0.03, 0.16-0.5 and 3.6-4.6 mg manganese plus dietary manganese. There was no difference in blood manganese levels in subjects from the 3 areas, but hair manganese was higher in subjects in the area with the highest level of manganese. It has been noted (US DHHS) that hair manganese is a useful measure of exposed versus unexposed populations but that it is of limited use in assessing individual exposure. The authors suggested that this could be because blood levels are highly variable and depend on how recent intake is, and thus could mask the influence of manganese stored in body tissues. A history was taken and a physical examination conducted by a neurologist unaware of the manganese exposure status. Neurological signs and symptoms were scored and were elevated in subjects from the highest manganese area. The symptoms scored ranged from depression, fatigue and hallucinations to tremor and impaired reflexes. Some of the symptoms were relatively subjective (e.g. fatigue) and it is uncertain whether one or two unusual 'outlier' individuals with a number of symptoms and/or signs may have produced the observed elevation in the high intake group. The authors noted that an effect was apparent at exposure levels which were negative in occupational studies. The authors attributed this finding to the age of the subjects, making them more susceptible to neuronal loss with ageing. The study was limited by inconsistent evidence of significant excess exposure and the subjective ascertainment of clinical effects.

Vieregge et al., 1995

This was a retrospective study of two cohorts exposed to water containing <0.05 mg/L or >0.3 mg/L (range 0.3-2.16 mg/L) manganese. The subjects in the two groups were aged 41-84 (mean = 57.5) years and 41-86 (mean 56.9) years. Long duration of exposure (10-40 years) to manganese had taken place. No estimates of the actual amount of water consumed or of the manganese content of the diet were

provided by the authors, but the cohorts were considered to be comparable. Assuming 2 L/day water consumption, manganese intakes of 0.1 and 4.3 mg from water can be estimated. A neurologist blinded to the group status of the participants conducted the examination. No significant differences in blood manganese levels or neurological scores were found between the two groups. The authors noted the conflict with the findings of Kondakis *et al.*, which they attributed to the greater age of the participants in that study. This study was also limited by the lack of exposure data.

Exposure assessment

Total exposure/intake:

Food	Mean: 4.9 mg/day 97.5th percentile: 8.2 mg/day (TDS, 1994)
Supplements	10 mg manganese/day (Annex 4)
Water	0.1 mg/day (assuming UK level of 0.05 mg/L and consumption of 2 L/day).
Estimated maximum intake:	8.2 mg + 10 mg + 0.1 mg = 18 mg/day

Tea drinkers are a potential high intake group, though the bioavailability of manganese in tea is unclear and may be low due to the presence of tannins.

Risk assessment

Cumulative exposure to manganese causes neurotoxicity in both humans and animals. Occupational exposure to manganese by inhalation has been associated with manganism, a condition similar to Parkinson's disease. This condition occurs as a result of inhalation exposure of high levels of manganese and is not relevant to the assessment of lower levels of manganese in food.

It has generally been considered that manganese uptake from oral exposure is subject to homeostatic control. However, there is also a suggestion of less severe neurotoxic effects at lower levels of exposure from consuming drinking water containing higher levels of manganese. The reported symptoms include muscle pain, fatigue, tremor, memory problems and impaired reflexes. Although other human data are available as noted above and in the review, it is not possible to draw conclusions from these due to problems with co-exposure, study design or lack of data.

Animal data are also available and indicate similar neurotoxic effects to those reported in humans. However, the neurotoxic effects are inevitably of a less subtle nature than the symptoms assessed in human studies and so these have not been considered further. Animal studies have also reported adverse effects on haematology and reproductive parameters.

ESTABLISHMENT OF GUIDANCE LEVEL

The data are insufficient to establish a Safe Upper Level for manganese.

Manganese is known to cause neurotoxicity at high levels of exposure. In humans, this occurs as a result of inhalation exposure. However, there is also a suggestion of less severe neurotoxic effects occurring at lower levels of exposure from the consumption of contaminated well or drinking water. Two large epidemiological studies show apparently conflicting results where subjects were exposed to water containing manganese at levels of 1.8-2.3 mg/L (Kondakis *et al.*, positive) and 0.3-2.1 mg/L (Vieregge *et al.*, negative). However, these studies may not be incompatible given the higher range of manganese levels measured in the Kondakis study and the greater age of the participants (increasing age theoretically conferring potentially greater vulnerability). A major limitation of both studies is the failure to provide water consumption or dietary manganese intake data. If it is assumed that water consumption is 2 L/day, the resulting intakes from water would have been approximately 3.6 – 4.6 and 0.6 – 4.4 mg/day. The contribution from food is more difficult to estimate. Little information on diet is provided in the Vieregge study. It should also be noted that the effect level in the Kondakis study is apparently lower than occupational exposure levels not associated with adverse effects. The authors considered that this may be due to the increased sensitivity of the ageing brain to manganese.

Other epidemiological studies suggest adverse effects at lower levels of manganese exposure but these are too limited in design to draw any conclusions. For guidance purposes, it is reasonable to assume that in the general population, a supplemental intake of up to 4 mg manganese/day in addition to the diet would be unlikely to produce adverse effects (equivalent to 0.07 mg/kg bw for a 60 kg adult) based on the NOAEL from the Vieregge study. No uncertainty factor is required as the NOAEL is based on a large epidemiological study. Using the NOAEL from the Kondakis study, it can be assumed that up to 0.5 mg/day manganese (equivalent to 0.008 mg/kg bw for a 60 kg adult) in addition to the diet would not result in adverse effects in older people. Assuming a dietary intake of 8.2 mg, acceptable total manganese intakes can be estimated to be 12.2 mg/day in the general population (equivalent to 0.2 mg/kg bw in a 60 kg adult) and 8.7 mg/day (equivalent to 0.15 mg/kg bw in a 60 kg adult) for older people.

Some population groups may be exposed to high levels of manganese as a result of tea consumption. The significance of this level of exposure is uncertain.

References

COMA (1998). Nutrition and Bone Health: with particular reference to calcium and vitamin D. Report of the Subgroup on Bone Health, Working Group on the Nutritional Status of the Population, Committee on Medical Aspects of Food and Nutrition Policy. The Stationery Office, London

Kondakis, X. G., Makris, N., Leotsinidis, M., Prinou, M., Papapetropoulos, T. (1989) Possible health effects of high manganese concentration in drinking water. *Archives of Environmental Health* **44**, 175-178

US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (1997). Draft toxicological profile for manganese update

Vieregge, P., Heinzow, B., Korf, G., Teichert, H.F., Schleifenbaum, P., Mosinger, H.U. (1995) Long term exposure to manganese in rural well water has no neurological effects. *Canadian Journal of Neurological Sciences* **22**, 286-289