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Manganese in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Rev/1: Revisions indicated with a vertical line in the left margin.

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Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

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The current version of Manganese in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is a revision of the background document prepared for an earlier edition of the Guidelines by Dr J. Du, United States Environmental Protection Agency.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2011. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

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Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

IOM	Institute of Medicine (USA)
LD_{50}	median lethal dose
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

1.1 Identity

Compound	*Chemical Abstracts Service No.*	*Molecular formula*
Manganese	7439-96-5	Mn
Manganese(II) chloride	7773-01-5	$MnCl_2$
Manganese(II, III) oxide	1317-35-7	Mn_3O_4
Manganese dioxide	1313-13-9	MnO_2
Potassium permanganate	7722-64-7	$KMnO_4$
Manganese sulfate	7785-87-7	$MnSO_4$

Source: ATSDR (2000).

Manganese is one of the most abundant metals in Earth's crust, usually occurring with iron. It is a component of over 100 minerals but is not found naturally in its pure (elemental) form (ATSDR, 2000). Manganese is an element essential to the proper functioning of both humans and animals, as it is required for the functioning of many cellular enzymes (e.g. manganese superoxide dismutase, pyruvate carboxylase) and can serve to activate many others (e.g. kinases, decarboxylases, transferases, hydrolases) (IPCS, 2002). Manganese can exist in 11 oxidative states; the most environmentally and biologically important manganese compounds are those that contain Mn^{2+}, Mn^{4+} or Mn^{7+} (USEPA, 1994).

1.2 Physicochemical properties

The physical and chemical properties of different manganese compounds vary substantially. These characteristics in turn determine the environmental behaviour and fate, exposure potential and subsequent toxicological potential of each compound.

Property	*Mn*	*$MnCl_2$*	*Mn_3O_4*	*MnO_2*	*$KMnO_4$*	*$MnSO_4$*
Melting point (°C)	1244	650	1564	Loses oxygen at 535 °C	Decomposes at <240 °C	700
Boiling point (°C)	1962	1190	No data	No data	No data	Decomposes at 850 °C
Density (g/cm^3)	7.21–7.44	2.98	4.86	5.03	2.70	3.25
Water solubility (g/l)	Decom-poses	723 (25 °C)	Insoluble	Insoluble	63.8 (20 °C)	520 (5 °C) 700 (70 °C)

Source: ATSDR (2000)

1.3 Organoleptic properties

At concentrations exceeding 0.1 mg/l, the manganese ion imparts an undesirable taste to beverages and stains plumbing fixtures and laundry (Griffin, 1960). When manganese(II) compounds in solution undergo oxidation, manganese is precipitated,

resulting in encrustation problems. At concentrations as low as 0.02 mg/l, manganese can form coatings on water pipes that may later slough off as a black precipitate (Bean, 1974). A number of countries have set standards for manganese of 0.05 mg/l, above which problems with discoloration may occur.

1.4 Major uses

Manganese is used principally in the manufacture of iron and steel alloys and manganese compounds and as an ingredient in various products (IPCS, 1999; ATSDR, 2000). Manganese dioxide and other manganese compounds are used in products such as batteries, glass and fireworks. Potassium permanganate is used as an oxidant for cleaning, bleaching and disinfection purposes (ATSDR, 2000; HSDB, 2001). Manganese greensands are used in some locations for potable water treatment (ATSDR, 2000). An organic manganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT), is used as an octane-enhancing agent in unleaded petrol in Canada, the United States of America (USA), Europe, Asia and South America (Lynam et al., 1999). Other manganese compounds are used in fertilizers, varnish and fungicides and as livestock feeding supplements (HSDB, 2001).

1.5 Environmental fate

Manganese compounds may be present in the atmosphere as suspended particulates resulting from industrial emissions, soil erosion, volcanic emissions and the burning of MMT-containing petrol (IPCS, 1999). In surface waters, manganese occurs in both dissolved and suspended forms, depending on such factors as pH, anions present and oxidation–reduction potential (ATSDR, 2000). Anaerobic groundwater often contains elevated levels of dissolved manganese. The divalent form (Mn^{2+}) predominates in most water at pH 4–7, but more highly oxidized forms may occur at higher pH values or result from microbial oxidation (ATSDR, 2000). Manganese can be adsorbed onto soil, the extent of adsorption depending on the organic content and cation exchange capacity of the soil. It can bioaccumulate in lower organisms (e.g. phytoplankton, algae, molluscs and some fish) but not in higher organisms; biomagnification in food-chains is not expected to be very significant (ATSDR, 2000).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Levels of manganese compounds in air vary widely depending on the proximity of point sources, such as ferroalloy production facilities, coke ovens and power plants. Average manganese levels in ambient air near industrial sources have been reported to range from 220 to 300 ng/m^3, whereas manganese levels in urban and rural areas without point sources have been reported to range from 10 to 70 ng/m^3 (Barceloux, 1999). Existing data indicate that little difference is found between manganese levels in ambient air in areas where MMT is used in the petrol and air levels in areas where MMT is not used (Lynam et al., 1999). The United States Environmental Protection Agency (USEPA, 1990) estimated the average annual background concentration of

manganese in urban areas to be 40 ng/m^3, based on measurements in 102 cities in the USA.

2.2 Water

Manganese occurs naturally in many surface water and groundwater sources and in soils that may erode into these waters. However, human activities are also responsible for much of the manganese contamination in water in some areas.

A survey of snow samples near an urban expressway in Montreal, Canada (where MMT is used in petrol), was unable to establish an association between automobile emissions and manganese concentrations in the snow (Loranger et al., 1996). Loranger et al. (1994) found ambient manganese concentrations to be significantly correlated with traffic density. Areas of intermediate and high traffic densities in Montreal had ambient manganese concentrations above the natural background level of 40 ng/m^3 (Loranger & Zayed, 1994; Loranger et al., 1994).

Ambient manganese concentrations in seawater have been reported to range from 0.4 to 10 µg/l (ATSDR, 2000), with an average of about 2 µg/l (Barceloux, 1999). Levels in fresh water typically range from 1 to 200 µg/l (Barceloux, 1999). ATSDR (2000) reported that a river water survey in the USA found dissolved manganese levels ranging from <11 to >51 µg/l. The United States Geological Survey's National Water Quality Assessment Program has gathered limited data since 1991 on representative study basins around the USA. These data indicate a median manganese level of 16 µg/l in surface waters, with 99th-percentile concentrations of 400–800 µg/l (Leahy & Thompson, 1994; USGS, 2001). Higher levels in aerobic waters are usually associated with industrial pollution.

The reducing conditions found in groundwater and some lakes and reservoirs favour high manganese levels; concentrations up to 1300 µg/l in neutral groundwater and 9600 µg/l in acidic groundwater have been reported (ATSDR, 2000). The National Water Quality Assessment Program data indicate that the 99th-percentile level of manganese in groundwater (5600 µg/l) is generally higher than that in surface waters, but the median level in groundwater (5 µg/l) is lower than that in surface water (USGS, 2001).

Overall, the detection frequency of manganese in groundwater in the USA is high (approximately 70% of sites) due to the ubiquity of manganese in soil and rock, but the levels detected in groundwater are generally below levels of public health concern (USEPA, 2002). Similarly, manganese is detected in about 97% of surface water sites (at levels far below those likely to cause health effects) and universally in sediments and tissues of aquatic biota (at levels that suggest that manganese does not bioaccumulate) (USEPA, 2002).

In the USA, the National Inorganic and Radionuclide Survey collected data from 989 community public water systems served by groundwater in 49 states between 1984 and 1986 and found that manganese was detected in 68% of the groundwater systems,

with a median concentration of 10 µg/l. Supplemental survey data from public water systems supplied by surface water in five states reported occurrence ranges similar to those of groundwater. In Germany, the drinking-water supplied to 90% of all households contained less than 20 µg of manganese per litre (Bundesgesundheitsamt, 1991).

2.3 Food

Manganese occurs naturally in many food sources, such as leafy vegetables, nuts, grains and animal products (IOM, 2002). Food is the most important source of manganese exposure in the general population (ATSDR, 2000; USEPA, 2002). Typical ranges of manganese concentrations in common foods are shown below:

Type of food	*Range of mean concentrations (mg/kg)*
Nuts and nut products	18.21–46.83
Grains and grain products	0.42–40.70
Legumes	2.24–6.73
Fruits	0.20–10.38
Fruit juices and drinks	0.05–11.47
Vegetables and vegetable products	0.42–6.64
Desserts	0.04–7.98
Infant foods	0.17–4.83
Meat, poultry, fish and eggs	0.10–3.99
Mixed dishes	0.69–2.98
Condiments, fats and sweeteners	0.04–1.45
Beverages (including tea)	0.00–2.09
Soups	0.19–0.65
Milk and milk products	0.02–0.49

Source: ATSDR (2000).

Heavy tea drinkers may have a higher manganese intake than the general population. An average cup of tea may contain 0.4–1.3 mg of manganese (ATSDR, 2000). In addition to dietary sources, approximately 12% of the adult population of the USA consumed manganese supplements in 1986 (Moss et al., 1989). The median intake of manganese in these dietary supplements was determined to be 2.4 mg/day, similar to the amount of the element consumed in the diet (based on information from the Third National Health and Nutrition Estimation Survey, held in 2001).

The hazard posed by overexposure to manganese must be weighed against the necessity for some minimum amount of manganese in the diet, because manganese is an essential nutrient, acting as a component of several enzymes and a participant in a number of important physiological processes. Freeland-Graves et al. (1987) suggested a range of 3.5–7 mg/day for adults based on a review of human studies. After

reviewing dietary surveys, Greger (1999) presented a range for average intakes from adult Western and vegetarian diets of 0.7–10.9 mg of manganese per day.

Infant formulas contain 50–300 µg of manganese per litre (Collipp et al., 1983), whereas human milk contains approximately 3.5–15 µg/l (USEPA, 1997; ATSDR, 2000). Assuming an intake of 742 ml of breast milk per day (USEPA, 1996), a breastfed infant would have an estimated daily manganese intake of 2.6–11.1 µg. An infant consuming the same volume of infant formula would have an estimated daily manganese intake of 37.1–223 µg. Assuming an average weight of 6 kg for an infant aged 6 months, the weight-adjusted average daily intake would range from 0.4 to 1.9 µg/kg of body weight per day for breastfed infants. The corresponding weight-adjusted intake for a formula-fed infant would be 6.2–37.2 µg/kg of body weight per day. Regarding the high manganese content of milk-based formula, the underexposure of infants to manganese appears less probable than their overexposure (Keen et al., 1986; Dörner et al., 1987; Davidsson et al., 1989a). Once solid foods are introduced, however, the contribution of manganese intake from milk becomes less significant.

In addition to manganese concentrations in food, an important consideration for determining human exposure to manganese in food is bioavailability. Several factors can influence the degree to which manganese in foods is absorbed upon ingestion. These include intake of dietary fibre, oxalic acids, tannins and phytic acids, which tend to decrease manganese absorption (Gibson, 1994; USEPA, 2002), as well as possibly sex-specific iron status (low iron can result in increased manganese absorption; Finley, 1999).

The Food and Nutrition Board of the Institute of Medicine (IOM, 2002) set adequate intake levels for manganese at 2.3 mg/day for men and 1.8 mg/day for women. Adequate intake levels for manganese were also set for other age groups; the values were 0.003 mg/day for infants from birth to 6 months, 0.6 mg/day for infants from 7 months to 1 year, 1.2 mg/day for children aged 1–3 years, 1.5–1.9 mg/day for children aged 4–13 years and 1.6–2.3 mg/day for adolescents and adults (IOM, 2002). The adequate intake for infants (newborn to 6 months) was set based on an average manganese concentration of 0.0035 mg/l in human milk and an average milk consumption of 0.78 litres/day. The manganese concentration in human milk varies. For example, manganese concentrations in human milk have been found to range from 0.003 to 0.01 mg/l (ATSDR, 2000) and from 0.007 to 0.015 mg/l (USEPA, 1997). Assuming an intake of 0.78 litres of milk per day and concentrations in human milk ranging from 0.003 to 0.015 mg/l, an infant (0–6 months) would ingest 0.002–0.012 mg of manganese per day from human milk, the upper limit of which is higher than the adequate intake set by IOM (2002) (i.e. 0.003 mg/day).

The IOM also set a tolerable upper intake level at 11 mg/day for adults, based on a recent review (Greger, 1999; IOM, 2002) that stated that the average manganese intake for adults eating typical Western and vegetarian diets in various surveys ranged from 0.7 to 10.9 mg of manganese per day. Davis & Greger (1992) reported that women given daily supplements of 15 mg of manganese (as an amino acid–chelated

manganese supplement) for 90 days experienced no adverse effects other than a significant increase in lymphocyte manganese-dependent superoxide dismutase, a biomarker that increases in direct relation to manganese exposure (Greger, 1998, 1999).

WHO (1973) reviewed several investigations of adult diets and reported that the average daily consumption of manganese ranged from 2.0 to 8.8 mg/day. Higher manganese intakes were associated with diets high in whole-grain cereals, nuts, green leafy vegetables and tea. From manganese balance studies, WHO (1973) concluded that 2–3 mg of manganese per day is adequate for adults and 8–9 mg/day is "perfectly safe."

Evaluations of standard diets from the USA, the United Kingdom and the Netherlands reveal average daily intakes of 2.3–8.8 mg of manganese per day. Depending on individual diets, however, a normal intake may be well over 10 mg of manganese per day (Schroeder et al., 1966), especially for vegetarian diets.

2.4 Estimated total exposure and relative contribution of drinking-water

The greatest exposure to manganese is usually from food. Adults consume between 0.7 and 10.9 mg/day in the diet (Greger, 1999), with even higher intakes reportedly being associated with some vegetarian diets (Schroeder et al., 1966; Freeland-Graves et al., 1987).

Manganese intake from drinking-water is normally substantially lower than intake from food. At the median drinking-water level of 10 µg/l determined in the National Inorganic and Radionuclide Survey described above, the intake of manganese would be 20 µg/day for an adult, assuming a daily water intake of 2 litres. Drinking mineral water regularly can add significantly to manganese intake (Dieter et al., 1992). Exposure to manganese from air is generally several orders of magnitude less than that from the diet, typically around 0.04 ng/day on average (USEPA, 1990), although this can vary substantially depending on proximity to a manganese source.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Absorption of manganese across the gastrointestinal tract is regulated by normal physiological processes to help maintain manganese homeostasis. A 7-week study in which seven adult male volunteers ingested high-fibre diets containing 12.0–17.7 mg of manganese per day (0.17–0.25 mg/kg of body weight per day) found that an average of 7.7% ± 6.3% of the manganese was absorbed during weeks 5–7, with no measurable net retention of manganese (Schwartz et al., 1986). Similarly, an average absorption of 8.4% ± 4.7% was observed in seven adults ingesting infant formula containing manganese (Sandström et al., 1986). Johnson et al. (1991) studied the absorption of radiolabelled manganese from various plant foods in adult men and women and reported that the absorption ranged from 1.4% to 5.5% and was significantly lower than the mean values of 7.8–10.2% from controls (manganese(II)

chloride dissolved in water). Manganese absorption may be higher in young animals and infants (Keen et al., 1986).

As mentioned above, several factors can influence the degree to which manganese in foods is absorbed upon ingestion. These include intake of dietary fibre, oxalic acids and phytic acids, which tend to decrease manganese absorption (Gibson, 1994; USEPA, 2002). The absorption of manganese is also closely linked to iron absorption; iron-deficient diets lead to an increased absorption of both iron and manganese (Thomson et al., 1971; Sandström et al., 1986; Finley, 1999). Absorption is also related inversely to the level of calcium in the diet (Schroeder et al., 1966; McDermott & Kies, 1987; Lutz et al., 1993). Certain constituents of tea, such as tannins, can result in reduced manganese absorption (Freeland-Graves & Llanes, 1994).

Some constituents of both infant formula and breast milk may also affect manganese bioavailability. Formula made from soy protein contains high levels of phytic acids and vegetable proteins, which probably decrease manganese bioavailability. Data from Keen et al. (1986) indicate that overall uptake of manganese from soy formula in rat pups was much greater than that from human milk or cow's milk, even though fractional manganese absorption was lowest in the soy formula, because formula contains much more manganese than human milk does. If the formula is also iron-fortified, manganese bioavailability may be further decreased, although studies on the inhibitory influences of iron have produced conflicting results (Freeland-Graves, 1994). Davidsson et al. (1989a) reported that the fractional absorption of manganese in adult humans given human milk (8.2%) was significantly higher than absorption from cow's milk (2.4%) and soy formula (0.7%). Manganese in infant formula is in the divalent state (Mn^{2+}), the absorption of which cannot be regulated by the lactoferrin receptors in the gut; breast milk manganese is in the trivalent form bound to lactoferrin, and its absorption is thus regulated (USEPA, 1997). Davidsson et al. (1989a) suggested that the lactoferrin in human milk as well as the higher calcium content in cow's milk contributed to the difference in absorption. Therefore, many factors probably control manganese absorption from infant formula, and firm conclusions are difficult to make in the absence of further data.

It should be noted that Davidsson et al. (1989a) performed their studies in adults; manganese body burden in infants may be influenced by the fact that the biliary excretion system, which is the primary route of manganese excretion, is not completely developed in human infants (Lönnerdal, 1994). Dörner et al. (1989) reported high retention of manganese in infants ingesting both human milk and cow's milk formulas. Studies in rats have demonstrated that young animals absorb significantly more manganese in the gut than do mature animals (Lönnerdal et al., 1987). Also, experimental animal studies have shown that manganese crosses the blood–brain barrier in neonates at a rate 4 times higher than that in adults (Mena, 1974). The relevance of these studies to humans is unknown, however, and few direct absorption data for manganese in human infants are available. Evidence exists, however, to indicate that infants are less well protected than adults against manganese overload. The manganese contents of erythrocytes in infants up to the age of 6 weeks

are higher by about 7–9% than those in adults (Hatano et al., 1985). Collipp et al. (1983) reported manganese levels in hair that increased significantly from birth (0.19 µg/g) to 6 weeks (0.865 µg/g) and 4 months (0.685 µg/g) of age in infants given formula, whereas infants given breast milk exhibited no significant increase (0.330 µg/g at 4 months). This study also reported that the average manganese level in hair in children exhibiting learning disabilities was significantly increased (0.434 µg/g) compared with that in children who exhibited normal learning ability (0.268 µg/g). It should be noted that the Collipp et al. (1983) study did not indicate that the increased manganese level in hair was from ingested manganese.

Manganese is present in all tissues of the body, the highest levels usually being found in the liver, kidney, pancreas and adrenals (Tipton & Cook, 1963; Sumino et al., 1975). It accumulates preferentially in certain regions of the brain in infants and young animals (Zlotkin & Buchanan, 1986; Kontur & Fechter, 1988).

Manganese is almost entirely excreted in the faeces, only a small proportion (0.1–2%) being eliminated in the urine (Davis & Greger, 1992). Faecal manganese is composed of unabsorbed dietary manganese plus manganese excreted in bile. In humans, elimination is biphasic, with half-lives of 13 and 37 days (Sandström et al., 1986; Davidsson et al., 1989b). Sweat, hair and the milk of lactating mothers also contribute to excretion (Roels et al., 1992).

Possible indicators of manganese exposure are the blood, with background levels ranging from 6.7 to 7.6 µg/ml (Roels et al., 1992; Mergler et al., 1994; Loranger & Zayed, 1995), and perhaps the hair (Fergusson et al., 1983; Chutsch & Krause, 1987). Manganese levels in blood do not provide data on long-term exposure. However, the blood platelet monoamine oxidase should be taken into consideration as an early biochemical indicator for adverse oxidative effects of manganese (Benedetti & Dostert, 1989; Humfrey et al., 1990).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

ATSDR (2000) noted that the acute lethality of manganese in animals appears to vary depending on the chemical species and whether exposure is via gavage or dietary ingestion. Single-dose oral median lethal dose (LD_{50}) values in adult rats exposed by gavage ranged from 331 mg of manganese per kilogram of body weight per day (as manganese chloride) (Kostial et al., 1989) to 1082 mg of manganese per kilogram of body weight per day (as manganese acetate) (Smyth et al., 1969), whereas 14-day exposure of rats to 1300 mg of manganese per kilogram of body weight per day (as manganese sulfate) in feed resulted in no deaths (NTP, 1993).

4.2 Short-term exposure

The central nervous system is the chief target of manganese toxicity. Oral doses ranging from 1 to 150 mg/kg of body weight per day produced a number of

neurological effects in rats and mice, mainly involving alterations in neurotransmitter and enzyme levels in the brain. These changes were sometimes accompanied by clinical signs, such as incoordination and changes in activity level (ATSDR, 2000). Deskin et al. (1980) reported an increase in monoamine oxidase activity in the hypothalamus in rats intubated with a daily dose of 20 mg of manganese per kilogram of body weight per day from birth to 24 days of age. Gastric irritation in the form of patchy necrosis of the epithelium was observed in guinea-pigs administered 10 mg of manganese per kilogram of body weight per day via gavage for 30 days (Chandra & Imam, 1973); the method of administration might have contributed to the observed effects, however. Male mice fed high doses of manganese in food for 13 weeks exhibited mild hyperplasia and hyperkeratosis of the forestomach; no effects were seen in female mice or male and female rats (NTP, 1993).

4.3 Long-term exposure

Chronic ingestion of 1–2 mg of manganese per kilogram of body weight per day produced changes in appetite and reduction in haemoglobin synthesis in rabbits, pigs and cattle (Hurley & Keen, 1987). Transient effects on biogenic amine levels and activities of dopamine β-hydroxylase and monoamine oxidase in rat brain have been noted with long-term exposures to manganese (Lai et al., 1984; Eriksson et al., 1987; Subhash & Padmashree, 1990). An increase in physical activity level and a transient increase in dopaminergic function were observed in rats given 40 mg of manganese per kilogram of body weight per day for 65 weeks (Nachtman et al., 1986). Two-year oral exposures to extremely high doses (1800–2250 mg/kg of body weight per day as manganese(II) sulfate) in male and female mice resulted in hyperplasia, erosion and inflammation of the forestomach; no effects were seen in rats (NTP, 1993).

Neurotoxicity is a known effect of long-term exposure to inhaled manganese in humans and animals, but the potential for neurotoxicity resulting from oral exposure is less well characterized. Muscular weakness and lower limb rigidity were observed in four male rhesus monkeys given oral doses of 6.9 mg of manganese per kilogram of body weight per day (as manganese chloride) for 18 months (Gupta et al., 1980). Degenerated neurons in the substantia nigra were observed at autopsy.

4.4 Reproductive and developmental toxicity

The results of several studies in rats and mice indicate that the ingestion of manganese can delay reproductive maturation in male animals (ATSDR, 2000). Testosterone levels were reduced in male rats given an oral dose of 13 mg of manganese per kilogram of body weight per day for 100–224 days (Laskey et al., 1982), whereas delayed growth of the testes was observed in young rats ingesting 140 mg of manganese per kilogram of body weight per day for 90 days (Gray & Laskey, 1980). These effects do not appear to be severe enough to affect male reproductive function (ATSDR, 2000). Several studies that found effects on male reproductive organs, however, did not assess reproductive performance (IPCS, 1999).

The results of most studies indicate that oral exposure to manganese does not result in reproductive toxicity in the female rodent (e.g. rats and mice) and rabbit (ATSDR, 2000), although increased post-implantation loss was observed in female rats in at least one study (Szakmáry et al., 1995). Results from several developmental studies in rodents and rabbits are equivocal. Data from the majority of these studies indicate that manganese exposure during part or all of gestation results in increased manganese levels in the pups (Järvinen & Ahlström, 1975; Kontur & Fechter, 1988) but generally causes 1) no measurable effect (Grant et al., 1997), 2) transient effects such as weight decreases and hyperactivity (Pappas et al., 1997) or 3) self-correcting effects on skeletal and organ development (Szakmáry et al., 1995). Studies involving oral exposures to manganese in drinking-water or by gavage in neonatal pups have reported changes in brain neurochemistry but generally do not show effects on neurological development (ATSDR, 2000). The data from one recent study indicate that rodent pups administered 22 mg of manganese per kilogram of body weight per day in drinking-water from birth to weaning (21 days) resulted in changes in brain neurochemistry and evoked sensory response (Dorman et al., 2000).

4.5 Mutagenicity and related end-points

The genotoxic potential of manganese in humans is not known (IPCS, 1999). Laboratory evidence for the mutagenicity and genotoxicity of manganese is equivocal. In vitro bacterial gene mutation tests have yielded both positive and negative results, whereas in vitro tests with fungi and mammalian cells have been predominantly positive. In vivo rat studies have been negative, and in vivo mouse studies have been positive (ATSDR, 2000). Manganese chloride produced an increased frequency of mutations in *Salmonella typhimurium* strain TA1537, but negative results in other strains; manganese sulfate was reported to be both positive and negative in separate studies in *Salmonella* strain TA97, but negative in other strains (IPCS, 1999). Positive results were obtained with various manganese compounds in *Photobacterium fischeri* and *Escherichia coli*, as well as in *Saccharomyces cerevisiae*, mouse lymphoma cells and hamster embryo cells (ATSDR, 2000). Manganese sulfate and potassium permanganate have been shown to increase sperm head abnormalities in vivo and increased the number of chromosomal aberrations and micronuclei in rat bone marrow (ATSDR, 2000). In spite of these results, the genotoxic potential of manganese in humans is not known (IPCS, 1999).

4.6 Carcinogenicity

No studies are available on the potential carcinogenicity of manganese following inhalation or dermal exposure in humans or experimental animals (ATSDR, 2000). A 2-year oral study of manganese sulfate in rats and mice produced equivocal evidence of carcinogenicity (NTP, 1993). In rats fed manganese sulfate (30–331 mg of manganese per kilogram of body weight per day in males, 26–270 mg of manganese per kilogram of body weight per day in females), no treatment-related increases in tumour incidence were reported. In mice fed manganese sulfate (63–722 mg of manganese per kilogram of body weight per day in males, 77–905 mg of manganese per kilogram of body weight per day in females), the incidence of follicular cell

adenoma of the thyroid was increased slightly in high-dose animals compared with controls. These increases were not statistically significant, and the tumours were observed at the end of the study only. However, follicular cell adenoma of the thyroid appears with low frequency in historical control male mice of this strain. Thus, the significance of these results and their relevance to normal human exposure to manganese are questionable.

5. EFFECTS ON HUMANS

Manganese is an essential element for many living organisms, including humans. For example, some enzymes require manganese (e.g. manganese superoxide dismutase), and some are activated by the element (e.g. kinases, decarboxylases). Adverse health effects can be caused by inadequate intake or overexposure. Manganese deficiency in humans appears to be rare, because manganese is present in many common foods. Animals experimentally maintained on manganese-deficient diets exhibit impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn and defects in lipid and carbohydrate metabolism (USEPA, 1984; Hurley & Keen, 1987).

The neurological effects of inhaled manganese have been well documented in humans chronically exposed to elevated levels in the workplace (Canavan et al., 1934; Cook et al., 1974; Roels et al., 1999; ATSDR, 2000). The syndrome known as "manganism" is caused by exposure to very high levels of manganese dusts or fumes and is characterized by a "Parkinson-like syndrome", including weakness, anorexia, muscle pain, apathy, slow speech, monotonous tone of voice, emotionless "mask-like" facial expression and slow, clumsy movement of the limbs. In general, these effects are irreversible. Some motor functions may already be affected following chronic exposure to levels of manganese of ≤ 1 mg/m^3 (if the inhaled manganese is respirable), but individuals in these situations have not shown the overt, clinical symptoms of those exposed to much higher levels (Roels et al., 1992; Mergler et al., 1994).

From animal experiments, it is known that inhaled manganese (even the insoluble manganese dioxide) is transported in a retrograde direction from the olfactory epithelium to the striatum of the brain (Gianutsos et al., 1997; Roels et al., 1997). During its uptake through the olfactory nerve endings (Tjälve et al., 1996; Brenneman et al., 2000; Vitarella et al., 2000; Bench et al., 2001), it may damage the astrocytes (Henriksson & Tjälve, 2000). After peroral uptake, manganese, like all other metals, is filtered from the blood by the choroid plexus (Zheng et al., 1991; Ingersoll et al., 1995). The retrograde transport of manganese through the olfactory epithelium directly into certain regions of the central nervous system or the brain could explain why the safe dose is much lower following inhalation exposure than after oral ingestion (Wang et al., 1989).

By the oral route, manganese is often regarded as one of the least toxic elements, although there is some controversy as to whether the neurological effects observed with inhalation exposure also occur with oral exposure. Several case reports of oral exposure to high doses of manganese have described neurological impairment as an

effect, but the quantitative and qualitative details of exposure necessary to establish direct causation are lacking. An individual who took large mineral supplements over several years displayed symptoms of manganism (Banta & Markesbery, 1977). Another individual who ingested 1.8 mg of potassium permanganate per kilogram of body weight per day for 4 weeks developed symptoms similar to Parkinson disease 9 months later (Holzgraefe et al., 1986; Bleich et al., 1999).

An epidemiological study in Japan described adverse effects in humans consuming manganese dissolved in drinking-water, probably at a concentration close to 28 mg/l (Kawamura et al., 1941). The manganese was derived from 400 dry-cell batteries buried near a drinking-water well. Fifteen cases of poisoning were reported among 25 persons examined, with symptoms including lethargy, increased muscle tone, tremor and mental disturbances. The most severe effects were seen in elderly people; less severe effects were seen in younger people, and effects were absent in children aged 1–6 years. However, the level of exposure to manganese was poorly quantified, and the people were also exposed to high levels of zinc. The rapid onset and progression of the symptoms and the recovery of some patients prior to mitigation of the manganese-contaminated well water suggest that exposure to other chemicals may also have been a factor in the presentation of symptoms.

An epidemiological study was conducted in Greece to investigate the possible correlation between long-term (i.e. more than 10 years) manganese exposure from water and neurological effects in elderly people (Kondakis et al., 1989). The levels of manganese in the drinking-water of three different geographical areas were 3.6–14.6 µg/l in the control area and 81–253 µg/l and 1800–2300 µg/l in the test areas. The authors concluded that progressive increases in the manganese concentration in drinking-water are associated with a progressively higher prevalence of neurological signs of chronic manganese poisoning and higher manganese concentrations in the hair of older persons. However, no data were given on exposure from other sources such as food and dust, and little information was provided on nutritional status and other possible confounding variables.

The individuals examined in the Kondakis et al. (1989) study also had exposure to manganese in their diet. This was originally estimated to be 10–15 mg/day because of the high intake of vegetables (X.G. Kondakis, personal communication, 1990). This estimate was subsequently lowered to 5–6 mg/day (X.G. Kondakis, personal communication, 1993). Because of the uncertainty in the amount of manganese in the diet and the amount of water consumed, it is impossible to estimate the total oral intake of manganese in this study. These limitations preclude the use of this study to determine a quantitative dose–response relationship for the toxicity of manganese in humans.

Contrary to the above study, another long-term drinking-water study in a northern rural area of Germany (Vieregge et al., 1995) found no neurological effects of manganese at a level of at least 0.3 mg/l. No significant differences in neurological tests were found in older people (41 subjects older than 40 years with a mean age of 57.5 years) consuming well water containing at least 0.3 mg of manganese per litre

(0.3–2.16 mg/l) for 10–40 years. The control group (74 subjects, mean age 56.9 years) was exposed to water containing less than 0.05 mg of manganese per litre. Subjects of both groups were randomly selected and matched with respect to age, sex, nutritional habits and drug intake. However, like the Kondakis et al. (1989) study, this study lacks exposure data from other routes and sources, and the manganese concentration range in the water is very wide.

In one area of Japan, a manganese concentration of 0.75 mg/l in the drinking-water supply had no apparent adverse effects on the health of consumers (Suzuki, 1970). No signs of toxicity were observed in patients given 30 mg of manganese citrate (9 mg of manganese) per day for many months (Schroeder et al., 1966). The incidence of motor neuron disease in a small Japanese town was positively correlated with a significantly increased manganese concentration in local rice and a low magnesium concentration in the drinking-water (Iwami et al., 1994). The study did not provide good estimates of overall exposure to manganese in either the control population or the population with motor neuron disease; therefore, development of the disease could not be conclusively attributed to manganese exposure. The simultaneous exposure to manganese and the deficiency of other essential minerals were possibly the reasons for the enhanced incidence of neurotoxicological symptoms in Japan and in another population in Guam (Yoshida et al., 1988; Florence & Stauber, 1989). There was also some speculation on a link between mineral deficiency, enhanced oral manganese uptake and manganese-catalysed denaturation of copper-free prion protein to the pathogenic prion protein (Brown et al., 2000), which could contribute to the enhanced occurrence of some prion diseases in certain world regions (Purdey, 2000).

Adverse neurological effects (decreased performance in school and in neurobehavioural examinations of the World Health Organization core test battery) were reported in 11- to 13-year-old children who were exposed to excess manganese through ingestion of contaminated water and from wheat fertilized with sewage water (He et al., 1994; Zhang et al., 1995). The exposed and control groups were both from farming communities and were matched for age, sex, grade, family income level and parental education level. The average manganese concentration of the drinking-water of the exposed group was 0.241 mg/l compared with the control level of 0.04 mg/l. The total exposure data, including manganese exposure from food, water and air, exposure duration, the nutritional status of the children and other confounding factors were not well characterized. Therefore, it was not possible to establish a cause–effect link between ingestion of excess manganese and preclinical neurological effects in children. Oral uptake of environmental manganese together with a deficiency of other minerals was suggested as a possible contributory factor to explain the enhanced incidence of neurological symptoms in isolated populations on Guam and the Kii Peninsula in East Asia (Yoshida et al., 1988; Florence & Stauber, 1989; Iwami et al., 1994).

6. PRACTICAL CONSIDERATIONS

6.1 Analytical methods

Sensitive methods exist for measuring total manganese in biological and environmental samples, although distinguishing between different oxidation states of manganese is not possible (IPCS, 1999). Atomic absorption spectroscopy is used for determining manganese concentrations in biological samples (e.g. urine, faeces and hair) at a detection limit as low as 1 µg/l for urine and 0.2 µg/g for hair. The technique has also been used to analyse manganese concentrations in water samples at levels as low as 0.01 µg/l (ATSDR, 2000). Inductively coupled argon–plasma optical emission spectrometry has also been used to measure manganese concentrations in biological fluids, water, waste products and air and has a detection limit of around 1–2 µg/l for liquids and 5 µg/m^3 for air (ATSDR, 2000). Colorimetric methods are also used in water analysis and have detection limits of about 10 µg/l (ISO, 1986).

6.2 Treatment methods and performance

Manganese concentrations in drinking-water are easily lowered using common treatment methods. Oxidation and filtration are usually adequate to achieve a manganese concentration of 0.05 mg/l in drinking-water.

7. CONCLUSION

Experimental animal data, especially rodent data, are not desirable for human risk assessment, because the physiological requirements for manganese vary among different species. Further, rodents are of limited value in assessing neurobehavioural effects, because the neurological effects (e.g. tremor, gait disorders) seen in primates are often preceded or accompanied by psychological symptoms (e.g. irritability, emotional lability), which are not apparent in rodents. The only primate study (Gupta et al., 1980) is of limited use in a quantitative risk assessment, because only one dose group was studied in a small number of animals, and information on the manganese content in the basal diet was not provided.

While several studies have determined average levels of manganese in various diets, no quantitative information is available to indicate toxic levels of manganese in the diet of humans. Because of the homeostatic control that humans maintain over manganese, manganese is generally not considered to be very toxic when ingested with the diet.

A review of typical Western and vegetarian diets found average adult manganese intakes ranging from 0.7 to 10.9 mg/day (Greger, 1999; IOM, 2002). The upper range manganese intake value of 11 mg/day from dietary studies is considered a no-observed-adverse effect level (NOAEL). It is not believed that this amount of manganese in the diet represents an overexposure to the element (IOM, 2002).

A health-based value can be calculated using this upper range value. A tolerable daily intake (TDI) of 0.06 mg/kg of body weight can be calculated by dividing the NOAEL of 11 mg/day by an uncertainty factor of 3 (to allow for the possible increased bioavailability of manganese from water) and an adult body weight of 60 kg. The guideline value of 0.4 mg/l is then derived from the TDI by assuming an allocation of 20% of the TDI to drinking-water and consumption of 2 litres of drinking-water per day by a 60 kg adult. However, as this health-based value is well above concentrations of manganese normally found in drinking-water, it is not considered necessary to derive a formal guideline value.

It should be noted that the presence of manganese in drinking-water will be objectionable to consumers if the manganese is deposited in water mains and causes water discoloration. Concentrations below 0.05 mg/l are usually acceptable to consumers, although this may vary with local circumstances.

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