Chapter 6.8 Manganese

General description

Sources

Manganese (Mn) is an element widely distributed in the earth's crust. It is considered to be the twelfth most abundant element and the fifth most abundant metal. Manganese does not occur naturally in a pure state; oxides, carbonates and silicates are the most important manganese-containing minerals. The most common manganese mineral is pyrolusite (MnO_2), usually mined in sedimentary deposits by open-cast techniques. Manganese occurs in most iron ores. Its content in coal ranges from 6 µg/g to 100 µg/g; it is also present in crude oil, but at substantially lower concentrations *(1)*.

Manganese is mainly used in metallurgical processes, as a deoxidizing and desulfurizing additive and as an alloying constituent. It is also used in the production of dry-cell batteries, in chemical manufacturing, in the manufacture of glass, in the leather and textile industries, and as a fertilizer. Organic carbonyl compounds of manganese are used as fuel-oil additives, smoke inhibitors and anti-knock additives in petrol *(2)*.

Crustal manganese enters the atmosphere by a number of natural and anthropogenic processes, which include the suspension of road dusts by vehicles and wind erosion and the suspension of soils, particularly in agricultural, construction and quarrying activities. The resulting mechanically generated aerosols consist primarily of coarse particles ≥ 2.5 µm mass median aerodynamic diameter (MMAD). The smelting of natural ores and the combustion of fossil fuels also result in the ejection of crustal manganese to the atmosphere in the form of fume or ash in the fine-particle range (< 2.5 µm MMAD). The manufacture of ferroalloys and other industrial processes are major sources of manganese released to the atmosphere *(2)*.

Coarse particles of manganese tend to settle out near sources of pollution, but fine particulate manganese can be distributed very widely. The most common forms of manganese compounds in coarse particles of crustal origin are oxides or hydroxides of oxidation state +2, +3 or +4, and manganese carbonate. The manganese emitted by metallurgical processes consists of oxides. The manganese from combusted methylcyclopentadienyl manganese tricarbonyl (MMT), used in some countries as a fuel additive, is emitted primarily as Mn_3O_4 particles <1 µm MMAD. Minute amounts of organic manganese compounds such as MMT may be present in ambient air under certain conditions, but MMT itself is rapidly photodegraded to inorganic manganese in sunlight, with an estimated half-time of 10–15 seconds *(2)*.

Occurrence in air

Background manganese concentrations of 0.05–5.4 ng/m^3 over the Atlantic Ocean *(3)* and 0.01 ng/m^3 at the South Pole *(4)* have been reported. For the period 1979–1983, the median ambient concentration of particulate manganese with an MMAD =10 µm (PM_{10}) for sites in the US Environmental Protection Agency's Inhalable Particulate Network was approximately 20 ng/m^3, with a 10th percentile level of 10 ng/m^3 and a 99th percentile value of over

200 ng/m^3 *(5)*. In the Federal Republic of Germany, annual mean concentrations of manganese ranged between 3 ng/m^3 and 16 ng/m^3 in Frankfurt am Main and Munich *(6)*; in Belgium over the period 1972–1977, annual mean manganese concentrations of between 42 ng/m^3 and 456 ng/m^3 were reported *(7)*. The Environmental Agency of Japan reported an annual mean manganese concentration of about 20–800 ng/m^3 in Japanese cities, with maximum 24-hour concentrations of 2–3 µg/m^3 *(8)*. From these and other data it can be concluded that annual average levels of manganese in ambient air in areas remote from known sources range from approximately 10 ng/m^3 to 30 ng/m^3, whereas in urban and rural areas without major point sources of manganese pollution, annual averages are mainly in the range of 10–70 ng/m^3.

In the proximity of foundries, manganese concentrations may rise to an annual average of 200–300 ng/m^3 and, in the presence of ferro- and silico-manganese industries, to over 500 ng/m^3 *(9)*. In such places, the average 24-hour concentrations may exceed 10 µg/m^3. The highest concentrations of manganese in the working environment have been reported from manganese mines, ore-processing plants, dry-cell battery plants and ferro-manganese plants. In mining operations, manganese concentrations of up to 250 mg/m^3 or even higher have sometimes been found. In dry-cell battery and ferro-manganese plants, the concentrations of manganese in air are lower. Values of 5–8 mg/m^3, and occasionally up to 20 mg/m^3 or more, have been reported *(10)*.

The size of manganese particles in the atmosphere varies from place to place, depending on the dominant sources in an area. In ferro-manganese and dry-cell battery plants, small particles dominate the size distribution of manganese aerosols, whereas in mining operations larger particles are usually predominant. Based on dichotomous sampler data for 22 sites in the United States, the proportion of PM_{10} manganese in the fine-mode (< 2.5 µm MMAD) ranged from 3% to 66% *(11)*.

Particulate manganese is transported by air currents until it is removed from the atmosphere by either dry or wet deposition. Manganese deposition in dustfall is more than twice that in rainfall *(2)*.

Routes of exposure

Air

The degree of respiratory uptake of manganese by inhalation depends primarily on particle size, with fine particles being small enough to reach the alveoli and be absorbed into the bloodstream. Coarse particles tend to be removed from the respiratory tract by mucociliary action that results in their relatively rapid movement to the nasopharynx and ingestion. The water solubility of a manganese compound appears to affect the time course of respiratory tract absorption, but not necessarily the amount ultimately absorbed. One study found no difference between the absorption of 1-µm particles of $MnCl_2$ and Mn_2O_3 in healthy adults *(12)*. Another study found that, following intratracheal instillation of $MnCl_2$ and Mn_3O_4 in rats, the soluble chloride cleared four times faster than the insoluble oxide from the respiratory tract; despite this initial difference, however, after 2 weeks the amounts of labelled manganese in the respiratory tract were similar for the two compounds *(13)*. Extra-thoracic deposition is another possible route of exposure. Some studies have indicated that neurotoxic

metals such as aluminium and cadmium can be directly transported to the brain olfactory bulbs via nasal olfactory pathways *(14,15)*.

Drinking-water
Concentrations of manganese in fresh water may vary from less than one to several thousand micrograms per litre, although drinking-water generally contains less than 100 µg/litre *(16)*. In 100 of the largest cities in the United States, 97% of the surveyed public water supplies contained concentrations below 100 µg/litre *(2)*.

Food
Food generally constitutes a major source of manganese intake for humans, but concentrations in foodstuffs vary markedly. The highest concentrations are found in certain foods of plant origin, especially wheat and rice, with concentrations between 10 mg/kg and 100 mg/kg. Polished rice and wheat flour contain less manganese, because most of it is in the bran. High concentrations of manganese have been found in tea leaves. Eggs, milk, fruits and meat generally contain less than 1 mg manganese per kg of food *(2)*. In a study performed in Canada, it was estimated that, of people's total manganese intake via food, 54% came from cereals and 14% from potatoes; meat, fish and poultry provided only 2% of manganese intake *(17)*. However, manganese concentrations may differ for the same items in different countries and areas.

Studies indicate that dietary manganese intakes range from 1–2 mg/day in bland hospital diets to around 18 mg/day for diets consisting predominantly of vegetables, nuts and seeds *(18)*. Diets high in nuts and whole grains tend to be high in manganese, whereas highly processed foods tend to be low. In one study, the daily intake for children aged 3–5 years averaged 1.4 mg/day, and 2.18 mg/day for children aged 9–13 years *(19)*. The daily intake of manganese by bottle-fed and breastfed infants is very low because of the low concentrations of manganese in both breast-milk and cow's milk *(20)*, although infant formula concentrations may be 3–100 times those of breast-milk *(21)*.

Relative significance of different routes of exposure
In terms of environmental sources and pathways of exposure, dietary intake of manganese generally dominates other routes of manganese exposure. Assuming an air concentration of 50 ng/m^3 and 40% absorption, daily manganese intake by inhalation would be in the order of 400 ng/day (based on breathing 20 m^3 air per day). Water and food manganese concentrations may vary widely, and the percentage absorption may also vary considerably depending on several factors, including age *(22)*, iron status *(23)*, other nutrients in the diet *(24)*, individual differences *(25)* and the form of manganese *(26)*. Typically, about 3–8% of an ingested dose is absorbed, but this figure might be greater in young children. In general, manganese intakes are 0.1–24 µg/day for water and 2–8 mg/day for food.

Pharmacokinetics

Although the amount of manganese in air to which individuals are exposed may be small compared to the amounts ingested in the diet, the absorption and delivery of manganese to various target organs may be relatively greater by inhalation than by ingestion. Quantitative pharmacokinetic data directly comparing different routes of exposure are not available, but several experimental studies have demonstrated that tissue manganese levels are well regulated when the exposure is by ingestion. Very few cases of manganese toxicity by ingestion have been observed. When inhaled, however, manganese that enters the

bloodstream passes first to the brain before being processed by the liver. Depending on its ability to cross the blood-brain barrier, this manganese may reach areas of the central nervous system and produce the characteristic neurotoxic effects of manganese. Although manganese is eliminated primarily by biliary excretion, it appears that inhaled manganese may not be as well regulated by this mechanism as is ingested manganese. Much remains to be learned about the pharmacodynamics of inhaled vis-à-vis ingested manganese.

Experimental studies using radiolabelled manganese indicate that the metal is eliminated more slowly from the brain than from most other organs or the body as a whole. Pharmacokinetic analyses based on inhalation of manganese chloride by macaque monkeys indicated that clearance from the brain was slower than from the respiratory tract and that the rate of clearance depended on the route of exposure *(27)*. Brain half-times were 223–267 days after inhalation, versus 53 days following subcutaneous administration in macaque monkeys *(27)* or 54 days in humans given manganese intravenously *(28)*. These long half-times were thought to reflect both slower clearance of brain stores and replenishment from other organs, particularly the respiratory tract. In rats, labelled manganese was slower to clear from brain than from the respiratory tract *(13)*.

Several occupational physicians have reported large individual differences in workers' susceptibility to manganese intoxication, which might be due in part to differences in the ability to clear particulate manganese from the lung *(29)*. However, large differences between individuals in their absorption of ingested manganese have also been noted *(24)*. The basis for the wide range in individual susceptibility to manganese toxicity remains to be elucidated.

Possibly because of inter-individual differences, blood and urine concentrations of manganese have not so far been proven to be reliable biomarkers of exposure for individuals, although they have shown significant positive correlations with external exposure parameters on a group basis *(30)*. Some studies have found a correlation between exposure levels and hair manganese concentrations *(31)*, but other studies have shown no correlation between individual hair manganese levels and neurobehavioural effects *(32)*.

Health effects

The essentiality of manganese has been established beyond question in animals. Nutritional deficiencies in humans have not been identified, however, and no figure has been recommended for the required dietary intake of manganese *(33)*.

Various epidemiological studies of workers exposed to manganese at average levels below 5 mg/m^3 have shown neurobehavioural, reproductive, and respiratory effects, both by objective testing methods and by workers' self-reported symptoms on questionnaires *(30,34–36)*. Neurobehavioural effects generally have reflected disturbances in the control of hand movements (e.g. tremor, reduced hand steadiness) and/or the speed of movement (e.g. longer reaction time, slower finger-tapping speed). Reproductive effects have included a smaller number of children born to manganese-exposed workers compared to matched controls, and various self-reported symptoms of sexual dysfunction. In recent studies at low to moderate occupational exposure levels, respiratory effects have been reflected primarily in self-reported symptoms of respiratory tract illnesses rather than in differences between objective spirometric measurements in manganese-exposed and control workers. The lack of studies using more sensitive investigational methods and the existence of some limited evidence from

an epidemiological study of schoolchildren *(37)*, however, raise a degree of concern about pulmonary function effects in relation to lower-level manganese exposure.

Studies of the neuropathological bases for manganism have pointed to the involvement of the corpus striatum and the extrapyramidal motor system *(38–41)*. Neuropathological lesions have generally been associated with the basal ganglia, with neuronal degeneration in the putamen and globus pallidus *(27,42)*. Brain imaging studies have also recently begun to provide additional insight into the neuropathology of manganese toxicity *(43,44)*.

In terms of the neurochemistry of manganese toxicity, several studies have shown that dopamine levels are affected by manganese exposure in humans, monkeys and rodents, with various indications of an initial increase in dopamine followed by a longer-term decrease *(45–47)*. Some theories of manganese neurotoxicity have focused on the role of excessive manganese in the oxidation of dopamine, resulting in free radicals and cytotoxicity *(47,48)*. In addition, the fundamental role of mitochondrial energy metabolism in manganese toxicity has been indicated by various studies *(49,50)*. Some have suggested that the mitochondrial dysfunctional effects of manganese result in various oxidative stresses to cellular defence mechanisms (e.g. glutathione) and, secondarily, free radical damage to mitochondrial DNA *(51)*. In view of the slow release of manganese from mitochondria *(50)*, such an indirect effect would help account for a progressive loss of function in the absence of ongoing manganese exposure, as manganese toxicity may continue or worsen in humans despite termination of exposure *(28,29)*.

Some experimental evidence suggests that the mechanisms of manganese toxicity may depend on the oxidation state of manganese. However, both the trivalent (Mn^{3+}) and divalent (Mn^{2+}) forms have been demonstrated to be neurotoxic *(49)*. Also, both forms can cross the blood-brain barrier, although research suggests that Mn^{3+} is predominantly transported bound to the protein transferring *(52)*, whereas Mn^{2+} may enter the brain independently of such a transport mechanism *(53)*. It is not clear what role, if any, conversion to other oxidation states (e.g. oxidation of Mn^{2+} to Mn^{3+} or reduction of Mn^{4+} to Mn^{3+}) plays in the neurotoxicity of manganese.

Effects on experimental animals and *in vitro* test systems

Evidence from several laboratory animal studies supports findings in manganese-exposed humans. For example, inhaled manganese has been shown to produce significant alterations in dopamine levels in the caudate and globus pallidus of Rhesus monkeys *(46)* and behavioural changes in mice *(54)*. However, species differences may complicate interpretation of certain neurobehavioral findings in laboratory animals. Unlike primates, rodents do not have pigmented substantia nigra, which is a brain region of relatively high manganese uptake and involvement in consequent neurobehavioral dysfunction. Nevertheless, rodent and primate studies show various neurochemical, neuropathological and neurobehavioural effects resulting from manganese exposure. However, because most laboratory animal studies of manganese neurotoxicity involve exposure by routes other than inhalation, they are not described here.

Other endpoints of manganese toxicity have also been investigated with laboratory animal models of inhalation exposure. Experimental animal data qualitatively support human study findings, in that manganese exposure results in an increased incidence of:

1. pneumonia in rats exposed to 43–139 mg manganese per m^3 as MnO_2 (mean MMAD = 0.76 μm; mean standard geometric deviation (s_g) = 2.28) for 2 weeks *(55)*;
2. pulmonary congestion in monkeys exposed to 0.7 or 3.0 mg manganese per m^3 as MnO_2 (80% < 1 μm) for 5 months *(56)*;
3. pulmonary emphysema in monkeys exposed to 0.7–3.0 mg manganese per m^3 as MnO_2 (80% < 1 μm) for 10 months *(57)*; and
4. bronchiolar lesions in rats and hamsters exposed to 0.117 mg manganese per m^3 as Mn_3O_4 (0.29 μm) for 56 days *(58)*.

Also, bronchiolar epithelium inflammation, widespread pneumonia and granulomatous reactions were induced in rats administered 10 mg MnO_2 (80% < 1 μm) by intratracheal injection, and pulmonary oedema was induced in rats administered 5–50 mg $MnCl_2$ (as a 5% solution in saline) in the same fashion *(59)*. Nevertheless, no significant pulmonary effects were detected in other studies of rats and monkeys exposed to as much as 1.15 mg manganese per m^3 as Mn_3O_4 (equivalent aerodynamic diameter = 0.11 μm; s_g = 3.07) for 9 months *(60–62)* and rabbits exposed to as much as 3.9 mg manganese per m^3 as $MnCl_2$ (MMAD = 1 μm) for 4–6 weeks *(63)*.

Laboratory animal studies have also shown that inhaled manganese may increase susceptibility to infectious agents such as *Streptococcus pyogenes* in mice *(64)*, *Enterobacter cloacae* in guinea pigs *(65)*, *Klebsiella pneumonia* in mice *(66)* and *Streptococcus haemolyticus* in mice *(67)*. In general, manganese concentrations were relatively high (>10 mg/m^3) in these studies; nevertheless, based on the regression line of the relationship between concentration and mortality in manganese-exposed mice, exposure to 0.62 mg/m^3 would be expected to result in a mortality rate at least 10% greater than the control rate *(63)*.

The developmental effects of manganese have been investigated primarily from the viewpoint of the nutritional role of this element, and therefore have generally involved oral exposure. Some studies indicate that neonates of various species have a greater body burden of manganese than mature individuals, possibly because neonates do not develop the ability to eliminate manganese (and thereby maintain manganese homeostasis) until some time after birth *(45,68,69)*. Moreover, some evidence suggests that the neonate's inability to maintain manganese homeostasis is due to a limitation in the elimination of manganese rather than in its gastrointestinal absorption *(70)*, which would suggest a potentially greater vulnerability of young individuals to excessive manganese exposure regardless of the route of exposure.

Several studies have demonstrated neurochemical alterations in young rats and mice exposed postnatally to manganese by routes other than inhalation *(45,71–73)*. In the only known inhalation study of the developmental toxicity of manganese, female HA/ICR mice were exposed to MnO_2 for 7 hours/day, 5 days/week for 16 weeks prior to conception, and between gestational days 1 and 18 *(74)*. For the first 12 weeks, the air manganese concentration was 49 mg/m^3; all later exposures were at 85 mg/m^3. To separate prenatal and postnatal exposure effects, a cross-fostering design was used. Although mothers exposed to MnO_2 prior to conception produced significantly larger litters, prenatally exposed offspring showed reduced scores on various neurobehavioural activity measures and retarded growth that persisted into adulthood. Balance and coordination were affected by either gestational or postpartum exposure to MnO_2.

Effects on humans

Several epidemiological studies of workers have provided consistent evidence indicating that neurotoxicity is associated with low-level occupational manganese exposure. Roels et al.*(30)* conducted a cross-sectional study of neurobehavioural and other endpoints in Belgian workers. A group of 92 male alkaline battery plant workers exposed to MnO_2 dust were compared to a matched control group of 101 male workers without industrial manganese exposure. The geometric mean occupational-lifetime integrated respirable dust concentration was 793 µg manganese per m^3·years (range: 40–4433). The equivalent value for total dust was 3505 mg manganese per m^3·years (range: 191–27 465). The monitored concentrations were considered representative of the usual exposures of the workers because work practices had not changed during the preceding 15 years of the plant's operation. Because the respirable fraction (5-µm MMAD) is more representative of the toxicologically significant particles (i.e. the smaller inhaled particles that deposit predominantly in the lower respiratory tract), the respirable dust measurements were considered to be more accurate than total dust as an indicator of exposure in relation to the observed health effects. The manganese-exposed workers performed significantly worse than matched controls on several measures of neurobehavioural function, particularly eye-hand coordination, hand steadiness and visual reaction time.

Similar neurobehavioral impairments were also found in an earlier study by Roels et al. *(34)* of a different occupational population in Belgium exposed to mixed manganese oxides and salts at approximately the same levels of total dust (respirable dust was not measured). A study of manganese workers in Canada also indicated that, among other effects, performance on tests of the ability to make rapid alternating hand movements, to maintain hand steadiness, and to perform other aspects of fine motor control was significantly worse than in matched controls *(36)*. Workers in that study were exposed to an average respirable manganese dust concentration of 35 mg/m^3 at the time of the study, but earlier exposure levels had been somewhat higher. In addition, reports of a Swedish study of manganese-exposed steel workers provided compelling evidence of comparable neurobehavioural impairments, including slower reaction time and finger-tapping speed *(35,75,76)*. The median total dust concentration in the Swedish study was 140 mg/m^3, with respirable dust reported as constituting 20–80% of individual workers' total dust exposures. Thus, the lowest-observed-adverse-effect level (LOAEL) from this study would presumably be somewhat lower than that from Roels et al.*(30)*, but the exposure histories in the Swedish study were less fully characterized.

None of the investigators in the above studies reported a no-observed-adverse-effect level (NOAEL). If the period of occupational manganese exposure in the Roels et al.*(30)* study had been longer than the relatively short average duration of only 5.3 years, and if the age of the workers had been greater than the relatively young average age of 31.3 years, it is possible that the observed effects would have occurred at even lower levels of exposure. Some reports indicate that manganese toxicity may not be clinically evident until some years after exposure has occurred or terminated *(28,29),* while others point to a greater sensitivity of elderly persons compared to middle-aged or young adults, for acute as well as chronic manganese toxicity *(77)*.

It is possible that the compensatory or reserve capacity of certain neurological mechanisms may be stressed by manganese exposure earlier in life, with manifestations of impairments only becoming evident much later, perhaps at a geriatric stage *(*78*)*. One reason for the latter

concern is that Parkinson's disease is typically a geriatric disease, in which the symptoms are only seen when the loss of brain cells that produce dopamine (which is also apparently involved in manganese toxicity) reaches 80% or more. Indeed, some neurologists think that a long latency period of perhaps several decades may precede various parkinsonian syndromes. These points lead to a concern that if manganese reduces the compensatory or reserve capacity of the nervous system, parkinson-type effects might occur earlier in life than they would otherwise.

Because of the involvement of the dopaminergic system and extrapyramidal motor system in both Parkinson's disease and manganism, symptoms of the two diseases are somewhat similar, and several writers have suggested the possibility of a common etiology. Nevertheless, many neurological specialists make a clear distinction in the etiologies and clinical features of Parkinson's disease and manganism *(47,79)*.

Evaluation of human health risks

Exposure evaluation

In urban and rural areas without significant manganese pollution, annual averages are mainly in the range of 0.01–0.07 $\mu g/m^3$; near foundries the level can rise to an annual average of 0.2–0.3 $\mu g/m^3$ and, where ferro- and silico-manganese industries are present, to more than 0.5 $\mu g/m^3$, with individual 24-hour concentrations sometimes exceeding 10 $\mu g/m^3$.

Health risk evaluation

The toxicity of manganese varies according to the route of exposure. By ingestion, manganese has relatively low toxicity at typical exposure levels and is considered a nutritionally essential trace element. By inhalation, however, manganese has been known since the early nineteenth century to be toxic to workers. Manganism is characterized by various psychiatric and movement disorders, with some general resemblance to Parkinson's disease in terms of difficulties in the fine control of some movements, lack of facial expression, and involvement of underlying neuroanatomical (extrapyramidal) and neurochemical (dopaminergic) systems. Respiratory effects such as pneumonitis and pneumonia and reproductive dysfunction such as reduced libido are also frequently reported features of occupational manganese intoxication. The available evidence is inadequate to determine whether or not manganese is carcinogenic; some reports suggest that it may even be protective against cancer. Based on this mixed but insufficient evidence, the US Environmental protection Agency has concluded that manganese is not classifiable as to human carcinogenicity *(80)*. IARC has not evaluated manganese *(81)*.

Several epidemiological studies of workers have provided consistent evidence of neurotoxicity associated with low-level manganese exposure. Sufficient information was available to develop a benchmark dose using the study by Roels et al. *(30),* thereby obviating the need to account for a LOAEL to NOAEL extrapolation. With regard to exposure, both lifetime integrated respirable dust concentrations as well as current respirable dust concentrations were considered. Correlation between effects and exposure was strongest for eye–hand coordination with current concentration of respirable dust. From the data of Roels et al. *(30),* lower 95% confidence limits of the best concentration estimate giving respectively a 10% effect ($BMDL_{10}$) of 74 $\mu g/m^3$ and a 5% effect ($BMDL_5$) of 30 $\mu g/m^3$ were calculated *(82)*. Taking a conservative approach, the lower 95% confidence limit of the $BMDL_5$ values was chosen as representative of the NOAEL. $BMDL_5$ values for the other exposure measures

(time-integrated and average concentration of respirable dust) are not substantially different *(36).*

In evaluating the potential health risks associated with inhalation exposure to manganese, various uncertainties must be taken into consideration. Virtually all of the human health evidence is based on healthy, adult male workers; other, possibly more sensitive populations have not been adequately investigated. Also, the potential reproductive and developmental toxicity of inhaled manganese has not been fully investigated.

Guidelines

Based on neurotoxic effects observed in occupationally exposed workers and using the benchmark approach, an estimated NOAEL (the lower 95% confidence limit of the $BMDL_5$) of 30 $\mu g/m^3$ was obtained. A guideline value for manganese of 0.15 $\mu g/m^3$ was derived by dividing by a factor of 4.2 to adjust for continuous exposure and an uncertainty factor of 50 (10 for interindividual variation and 5 for developmental effects in younger children). This latter factor was chosen by analogy with lead, where neurobehavioural effects were found in younger children at blood lead levels five times lower than in adults, and supported by evidence from studies of experimental animals). The adjustment for continuous exposure was considered sufficient to account for long-term exposure based on knowledge of the half-time of manganese in the brain. The guideline value should be applied as an annual average.

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