Concise International Chemical Assessment Document 12

MANGANESE AND ITS COMPOUNDS

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

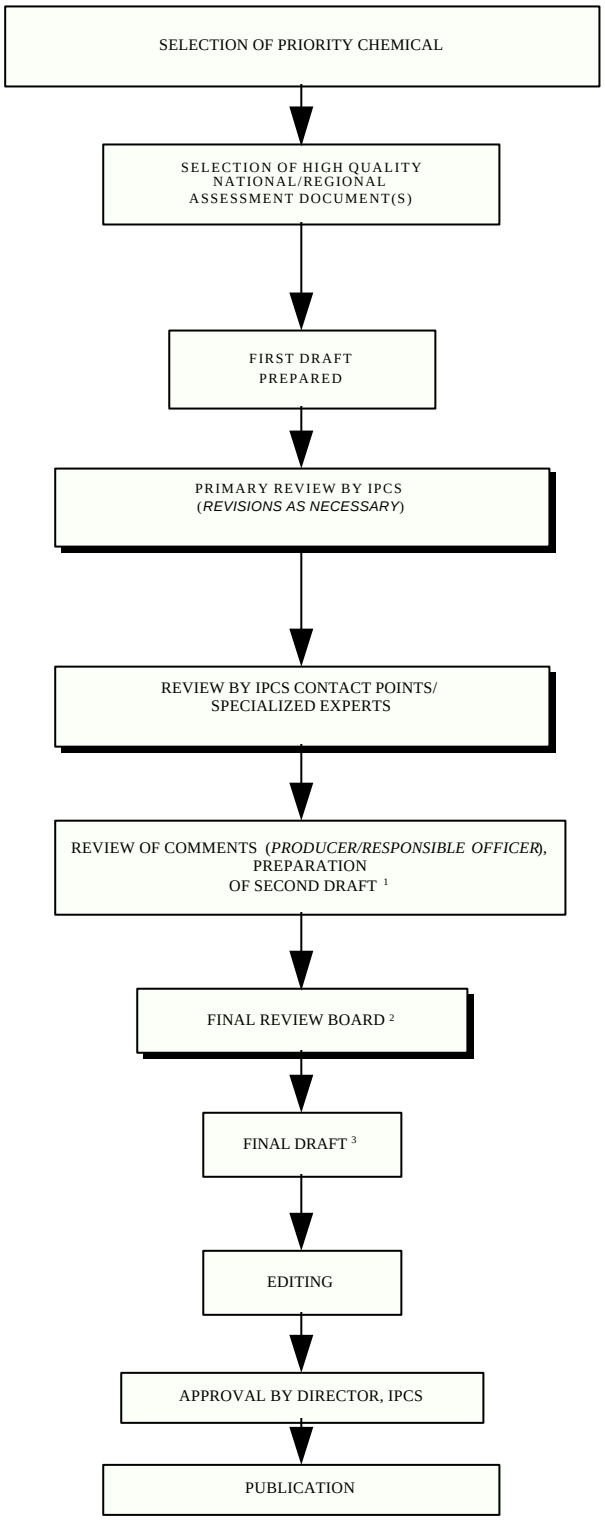
The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on manganese and its compounds was based principally on the report entitled *Toxicological profile for manganese (update), draft for public comment*, prepared by the Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services (ATSDR, 1996). Information contained in the Hazardous Substances Data Bank, developed and maintained by the National Library of Medicine, US Department of Health and Human Services, was also used (HSDB, 1998). Data identified as of November 1998 were considered in these source documents. Additional data came from other references, such as assessments prepared by the US Environmental Protection Agency (EPA) and the World Health Organization (WHO), as well as a variety of reports in the literature. The source documents used to develop this CICAD do not cover the effects of manganese on the ecological environment. No other sources (documents developed by a national organization and subject to rigorous scientific review) on this topic were identified. Therefore, this CICAD addresses environmental levels as a source of human exposure only. No attempt has been made in this document to assess effects on organisms in the environment. Information on the availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Berlin, Germany, on 26–28 November 1997. Participants at the Final Review Board meeting are presented in Appendix 3. The International Chemical Safety Card (ICSC 0174) for manganese, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Manganese (Mn) is a naturally occurring element that is found in rock, soil, water, and food. Thus, all humans are exposed to manganese, and it is a normal component of the human body. Food is usually the most important route of exposure for humans. Estimated Safe and Adequate Daily Intakes of 1–5 mg manganese have been established for children 1 year of age and older through to adults; these levels generally parallel amounts of the compound delivered via the diet.

Manganese is released to air mainly as particulate matter, and the fate and transport of the particles depend on their size and density and on wind speed and direction. Some manganese compounds are readily soluble in water, so significant exposures can also occur by ingestion of contaminated drinking-water. Manganese in surface water can oxidize or adsorb to sediment particles and settle to the bottom. Manganese in soil can migrate as particulate matter to air or water, or soluble manganese compounds can be leached from the soil.

Above-average exposures to manganese are most likely to occur in people who work at or live near a factory or other site where significant amounts of manganese dust are released into the air. In some regions, the general population can be exposed to manganese released into air by the combustion of unleaded gasoline containing the organomanganese compound methylcyclopentadienyl manganese tricarbonyl (MMT) as an antiknock ingredient. Some people can be exposed to excess manganese in drinking-water — for example, when manganese from batteries or pesticides leaches into well-water. Children can be exposed to excess manganese in soils through hand-to-mouth behaviour.

In humans, manganese is an essential nutrient that plays a role in bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from damaging free radical species, and the formation of glycosaminoglycans. However, exposure to high levels via inhalation or ingestion can cause adverse health effects. Given comparable doses, more manganese reaches the brain following inhalation than following ingestion, and most health effects are associated with chronic inhalation exposure. Little is known about the relative toxicity of different manganese compounds. However, available evidence indicates that various manganese compounds can induce neurological effects; these effects have been observed following chronic (365 days or more) inhalation exposures in humans and intermediate (15–364 days) and chronic oral exposures in animals.

In general, the available data indicate that exposure to excess manganese for 14 days or less (acute duration) or up to a year (intermediate duration) has an effect on the respiratory system and the nervous system, with little to no effect on other organ systems. Acute inhalation exposure to high concentrations of manganese dusts (specifically manganese dioxide [MnO_2] and manganese tetroxide [Mn_3O_4]) can cause an inflammatory response in the lung, which, over time, can result in impaired lung function. Lung toxicity is manifested as an increased susceptibility to infections such as bronchitis and can result in manganic pneumonia. Pneumonia has also been observed following acute inhalation exposures to particulates containing other metals. Thus, this effect might be characteristic of inhalable particulate matter and might not depend solely on the manganese content of the particle.

There are a few reports suggesting that intermediate inhalation exposure to manganese compounds produces effects on the central nervous system, but reliable estimates of exposure levels are not available. Inhalation studies in animals resulted in biochemical, respiratory, and neurobehavioural effects. However, a threshold for these effects has not been identified, because the expo-

sure levels associated with these effects range over an order of magnitude.

In chronic inhalation exposure to manganese, the main organ systems affected are the lungs, nervous system, and reproductive system, although effects on other organ systems have also been observed. A recurring manganic pneumonia and acute respiratory effects have been associated with chronic inhalation exposures to manganese. Effects on the nervous system include neurological and neuropsychiatric symptoms that can culminate in a Parkinsonism-like disease known as manganism; evidence suggests that laboratory animals, especially rodents, are not as sensitive as humans, and possibly other primates, to the neurological effects of inhalation exposure to manganese. Reproductive effects of chronic inhalation exposure to manganese include decreased libido, impotence, and decreased fertility in men; information is not available on reproductive effects in women. Studies in animals indicate that manganese can cause direct damage to the testes and late resorptions. Data from animal studies on the effects of inhaled manganese on the immunological system and the developing fetus are too limited to make firm conclusions on the significance of these effects for humans.

Information on the carcinogenic potential of manganese is limited, and the results are difficult to interpret with certainty. In rats, chronic oral studies with manganese sulfate ($MnSO_4$) showed a small increase in the incidence of pancreatic tumours in males and a small increase in pituitary adenomas in females. In other studies with manganese sulfate, no evidence for cancer was noted in rats and a marginally increased incidence of thyroid gland follicular cell adenomas was observed in mice. The results of *in vitro* studies show that at least some chemical forms of manganese have mutagenic potential. However, as the results of *in vivo* studies in mammals are inconsistent, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds.

Large oral doses of concentrated manganese salts given by gavage can cause death in animals, but oral exposures via food or water have not been found to cause significant toxicity over acute or short-term exposures. Similarly, parenteral administration of manganese salts can cause developmental toxicity, but effects were not found with oral exposure. Intermediate-duration oral exposure of humans to manganese has been reported to cause neurotoxicity in two cases, but the data are too limited to define the threshold or to judge if these effects were due entirely to the manganese exposure. Some data on neurological or other health effects in humans from chronic oral intake of manganese exist, but these studies are limited by uncertainties in the exposure routes and total exposure levels as well as by the existence of other confounding factors. The studies in humans and animals do not provide sufficient information to determine dose levels or effects of concern following chronic oral exposure. Thus, the available evidence for adverse effects associated with chronic ingestion of excess manganese is suggestive but inconclusive.

The dermal route does not appear to be of significant concern and has not been investigated to any extent. Available information is limited to reports on the corrosive effects of potassium permanganate ($KMnO_4$) and case reports of effects from dermal absorption of organic manganese compounds such as MMT.

From these data, it is clear that adverse neurological and respiratory effects from manganese exposure can occur in occupational settings. Limited evidence also suggests that adverse neurological effects can be associated with ingestion of excess manganese in environmental settings. As a result of predisposing factors, certain individuals might be more susceptible to adverse effects from exposure to excess manganese. These might include people with lung disease, people who are exposed to other lung irritants, neonates, older people, individuals with iron deficiency, or people with liver disease.

There are several approaches to the development of a guidance value for manganese in air. A recently developed guidance value of 0.15 ：g manganese/m^3 is highlighted here as one possible example; some additional approaches are also presented.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Table 1 lists common synonyms and other relevant information on the chemical identity and properties of manganese and several of its most important compounds. Manganese is a naturally occurring element that is found in rock, soil, water, and food. Manganese can exist in a number of oxidation states. Manganese and its compounds can exist as solids in the soil and as solutes or small particles in water. Most manganese salts are readily soluble in water, with only the phosphate and the carbonate having low solubilities. The manganese oxides (manganese dioxide and manganese tetroxide) are poorly soluble in water. Manganese can also be present in small dust-like particles in the air. Additional physical/chemical properties are presented in the International Chemical Safety Card (ICSC 0174) reproduced in this document.

Table 1: Chemical identity of manganese and its compounds.[a]

	Manganese	Manganous chloride	Manganese sulfate	Manganese(II, III) oxide	Manganese dioxide	Potassium permanganate	Methylcyclo-pentadienyl-manganese tricarbonyl[b]	Manganese ethylene-bis-dithiocarbamate	Mancozeb[c]
Synonyms	Elemental manganese; colloidal manganese; cutaval[d]	Manganese chloride[d]; manganese dichloride	Manganous sulfate; sulfuric acid manganese	Trimanganese tetroxide; mangano-manganic oxide[e]; manganese tetroxide	Manganese peroxide; manganese binoxide; manganese black; battery manganese	Permanganic acid, potassium salt[e]; chameleon mineral	MMT[f]; methyl-cymantrene; Antiknock-33; manganese tricarbonyl methyl-cyclopentadienyl	Trimangol 80; maneb[g]; ethylene-bis[dithiocarbamic acid], manganous salt; Dithane	Dithane M-45; manganese ethylenebis (dithiocarba-mate) (polymeric); Manzate; Man-zeb; Zimaneb
Chemical formula	Mn	$MnCl_2$	$MnSO_4$	Mn_3O_4	MnO_2	$KMnO_4$	$C_9H_7MnO_3$	$C_4H_6MnN_2S_4$	$C_4H_6MnN_2S_4$[j] $C_4H_6N_2S_4Zn$
CAS Number	7439-96-5	7773-01-5	7785-87-7	1317-35-7	1313-13-9	7722-64-7	12108-13-3	12427-38-2	12427-38-2
Molecular weight	54.94[e]	125.85[e]	151.00[e]	228.81[h]	86.94[e]	158.04[e]	218.10	265.31	541.03
Colour	Grey-white[h]	Pink[h]	Pale rose-red	Black[h]	Black	Purple	Dark orange-red[i]	Yellow-brown	Greyish-yellow
Physical state	Solid	Solid	Solid	Solid	Solid	Solid	Liquid[i]	Powder	Powder
Melting point	1244 °C[h]	650 °C	700 °C	1564 °C	535 °C[h]	<240 °C (decomposes)	No data	Decomposes on heating	Decomposes without melting
Boiling point	1962 °C[h]	1190 °C[h]	Decomposes at 850 °C	No data	No data	No data	232.8 °C[i]	No data	No data
Solubility	Dissolves in dilute mineral acids[h]; decomposes in water	Very soluble in water; soluble in alcohol	Soluble in water and alcohol	Insoluble in water; soluble in hydrochloric acid	Soluble in hydrochloric acid; insoluble in water	Soluble in water, acetone, and sulfuric acid	Practically insoluble in water (70 ppm at 25 °C); completely soluble in hydrocarbons	Slightly soluble in water; soluble in chloroform	Practically insoluble in water as well as most organic solvents

CAS = Chemical Abstracts Service

[a] Adapted from ATSDR (1996). All information obtained from Sax & Lewis (1987), except where noted.
[b] NTP (1999).
[c] Hamilton (1995).
[d] HSDB (1998).
[e] Windholz (1983).
[f] Zayed et al. (1994).
[g] Ferraz et al. (1988).
[h] Lide (1993).
[i] Verschueren (1983).

3. ANALYTICAL METHODS

Atomic absorption spectrophotometric analysis is the most widely used method for determining manganese in biological materials and environmental samples. Fluorimetric, colorimetric, neutron activation analysis, and plasma atomic emission techniques are also recommended for measuring manganese in such samples. Most of these methods require wet digestion, derivatization, and/or extraction before detection. In most cases, distinguishing between different oxidation states of manganese is impossible, so total manganese is measured.

The detection limits of these methods range from <0.01 to 0.2 μg/g for biological tissues and fluids, from 5 to 10 μg/m^3 for air, and from 0.01 to 50 μg/litre for water (Kucera et al., 1986; Abbasi, 1988; Lavi et al., 1989; Mori et al., 1989; Chin et al., 1992; ATSDR, 1996). Determination of manganese levels in soil, sludge, or other solid wastes requires an acid extraction/digestion step before analysis. The details vary with the specific characteristics of the sample, but treatment usually involves heating in nitric acid, oxidation with hydrogen peroxide, and filtration and/or centrifugation to remove insoluble matter (ATSDR, 1996).

A nuclear magnetic resonance method (Kellar & Foster, 1991) and a method using on-line concentration analysis (Resing & Mottl, 1992) were used to determine both free and complexed manganese ions in aqueous media. The latter method was highly sensitive, with a detection limit of 36 pmol/litre (1.98 ng/litre when concentrating 15 ml of seawater).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Manganese is ubiquitous in the environment. It comprises about 0.1% of the earth's crust (NAS, 1973; Graedel, 1978). Because manganese occurs in soil, air, water, and food, all humans are exposed to it. Manganese is a normal component of the human body, and food is usually the most important route of exposure for humans. Manganese does not occur naturally as a base metal but is a component of more than 100 minerals, including various sulfides, oxides, carbonates, silicates, phosphates, and borates (NAS, 1973). The most commonly occurring manganese-bearing minerals include pyrolusite (manganese dioxide), rhodocrosite (manganese carbonate), and rhodonite (manganese silicate) (NAS, 1973; Windholz, 1983; US EPA, 1984; HSDB, 1998).

The manganese content in ore produced worldwide was estimated to be 8.8 million tonnes in 1986. Production levels of manganese ore and its total manganese metal content remained nearly the same through 1990 (US Department of the Interior, 1993). Levels of ore produced worldwide in 1995, 1996, and 1997 declined slightly, with total manganese metal content declining proportionately to 8.0, 8.1, and 7.7 million tonnes, respectively (US Department of the Interior, 1996, 1998). Although modern steelmaking technologies call for lower unit consumption of manganese, worldwide demand for steel is projected to increase moderately in the future, particularly in developing countries (US Department of the Interior, 1995, 1998). Although manganese usage in other industries is increasing, this will have minor overall effect on manganese demand, and future trends for manganese are still expected to increase with demands for steel (EM, 1993; US Department of the Interior, 1995, 1998). The demand for manganese in other industries (e.g., dry-cell battery manufacturing) might also increase, but the overall effect of these other uses on global trends in manganese production and use is minor (US Department of the Interior, 1995, 1998).

Manganese compounds are produced from manganese ores or from manganese metal. The organomanganese compound MMT, an antiknock additive in unleaded gasoline, is produced by the reaction of manganese chloride ($MnCl_2$), cyclopentadiene, and carbon monoxide in the presence of manganese carbonyl (NAS, 1973; US EPA, 1984; Sax & Lewis, 1987; HSDB, 1998). Metallic manganese (ferromanganese) is used principally in steel production along with cast iron and superalloys to improve hardness, stiffness, and strength (NAS, 1973; US EPA, 1984; HSDB, 1998). Manganese compounds have a variety of uses. Manganese dioxide is commonly used in the production of dry-cell batteries, matches, fireworks, porcelain and glass-bonding materials, and amethyst glass; it is also used as the starting material for the production of other manganese compounds (NAS, 1973; Venugopal & Luckey, 1978; US EPA, 1984). Manganese chloride is used as a precursor for other manganese compounds, as a catalyst in the chlorination of organic compounds, in animal feed to supply essential trace minerals, and in dry-cell batteries (US EPA, 1984; HSDB, 1998). Manganese sulfate is used primarily as a fertilizer and as a livestock supplement; it is also used in some glazes, varnishes, ceramics, and fungicides (Windholz, 1983; US EPA, 1984; HSDB, 1998). Manganese ethylene-bis-dithiocarbamate (maneb) is widely applied to edible crops as a fungicide and is therefore a potential source of manganese in soil and in food crops (Ferraz et al., 1988; Ruijten et al., 1994). Potassium permanganate is used as an oxidizing agent; as a disinfectant; as an antialgal agent; for metal cleaning, tanning, and bleaching; as a purifier in water

and waste treatment plants; and as a preservative for fresh flowers and fruits (HSDB, 1998).

The main sources of manganese releases to the air are industrial emissions, combustion of fossil fuels, and re-entrainment of manganese-containing soils (Lioy, 1983; US EPA, 1983, 1984, 1985a, 1985b). Manganese can also be released to the air during other anthropogenic processes, such as welding and fungicide application (Ferraz et al., 1988; MAK, 1994; Ruijten et al., 1994). Total emissions to air from anthropogenic sources in the USA were estimated to be 16 400 t in 1978, with about 80% (13 200 t) from industrial facilities and 20% (3200 t) from fossil fuel combustion (US EPA, 1983). Air emissions by US industrial sources reported for 1987 totalled 1200 t (TRI87, 1989). In 1991, air emissions from facilities in the USA ranged from 0 to 74 t, with several US states reporting no emissions (TRI91, 1993). Air erosion of dusts and soils is also an important atmospheric source of manganese, but no quantitative estimates of manganese release to air from this source were identified (US EPA, 1984). Volcanic eruptions can also release manganese to the atmosphere (Schroeder et al., 1987).

In some countries, combustion of gasoline containing MMT contributes approximately 8% to levels of manganese tetroxide in urban air (Loranger & Zayed, 1995). MMT was used as a gasoline additive in the USA for a number of years, resulting in manganese emissions. Analysis of manganese levels in the air indicated that vehicular emissions contributed an average of 13 ng manganese/m^3 in southern California, whereas vehicular emissions were only about 3 ng/m^3 in central and northern California (Davis et al., 1988). A ban on MMT use as a fuel additive was imposed for a period of time, then lifted by the US EPA in 1995.

In Canada, MMT use as a fuel additive has gradually increased since 1976. Manganese emissions from gasoline combustion rose sharply from 1976 through the early 1980s, reaching an estimated 200.2 t by 1985 (Jacques, 1984). In 1990, lead was completely replaced by MMT in gasoline in Canada (Loranger & Zayed, 1994). MMT use peaked in 1989 at over 400 t, which was more than twice the usage in 1983 and 1.5 times the usage in 1986. MMT use declined to about 300 t by 1992, owing to reductions in its concentration in gasoline. However, ambient monitoring data for manganese in Canadian cities without industrial sources for the 1989–1992 period did not reflect this peak in MMT use. Air manganese levels ($PM_{2.5}$, or particulate matter with an aerodynamic diameter less than or equal to 2.5 ：m) remained constant at 0.11–0.013 ：g/m^3 for small cities and 0.020–0.025 ：g/m^3 for large cities (Health Canada, 1994; Egyed & Wood, 1996). Manganese emission levels can vary depending on the concentration of MMT in gasoline and gasoline usage patterns. One study reported a correlation between atmospheric manganese concentrations in 1990 air samples and traffic density in Montreal (Loranger et al., 1994). However, a later study by these investigators reported that atmospheric manganese concentrations in Montreal decreased in 1991 and 1992 despite an estimated 100% increase in manganese emission rates from MMT in gasoline (Loranger & Zayed, 1994). Another study suggested that the high manganese levels in Montreal were, in part, due to the presence of a silico- and ferro-manganese facility that ceased operation in 1991 (Egyed & Wood, 1996).

Manganese can be released to water by discharge from industrial facilities or as leachate from landfills and soil (US EPA, 1979, 1984; Francis & White, 1987; TRI91, 1993). In the USA, reported industrial discharges in 1991 ranged from 0 to 17.2 t for surface water, from 0 to 57.3 t for transfers to public sewage, and from 0 to 0.114 t for underground injection (TRI91, 1993). An estimated total of 58.6 t, or 1% of the total environmental release of manganese in the USA, was discharged to water in 1991 (TRI91, 1993).

Land disposal of manganese-containing wastes is the principal source of manganese releases to soil. In 1991, reported industrial releases to land in the USA ranged from 0 to 1000 t. More than 50% of the total environmental release of manganese (3753 t) was to land (TRI91, 1993).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Elemental manganese and inorganic manganese compounds have negligible vapour pressures but can exist in air as suspended particulate matter derived from industrial emissions or the erosion of soils. Manganese-containing particles are removed from the atmosphere mainly by gravitational settling or by rain (US EPA, 1984).

Soil particulate matter containing manganese can be transported in air. The fate and transport of manganese in air are largely determined by the size and density of the particle and wind speed and direction. An estimated 80% of the manganese in suspended particulate matter is associated with particles with a Mass Median Equivalent Diameter (MMED) of <5 ：m, and 50% of this manganese is estimated to be associated with particles that are <2 ：m in MMED. (Whether these data are for particles in urban or rural areas is unclear. However, it is known that the size of manganese particles in the air tends to vary by source; small particles dominate around

ferromanganese and dry-cell battery plants, whereas large particles tend to predominate near mining operations [WHO, 1999].) Based on these data, manganese's small particle size is within the respirable range, and widespread airborne distribution would be expected (WHO, 1981). Very little information is available on atmospheric reactions of manganese (US EPA, 1984). Although manganese can react with sulfur dioxide and nitrogen dioxide, the occurrence of such reactions in the atmosphere has not been demonstrated.

The transport and partitioning of manganese in water are controlled by the solubility of the specific manganese compound present. In most waters (pH 4–7), Mn(II) predominates and is associated principally with carbonate, which has relatively low solubility (US EPA, 1984; Schaanning et al., 1988). The solubility of Mn(II) can be controlled by manganese oxide equilibria (Ponnamperuma et al., 1969), with manganese being converted to other oxidation states (Rai et al., 1986). In extremely reduced water, the fate of manganese tends to be controlled by the formation of the poorly soluble sulfide (US EPA, 1984). In groundwater with low oxygen levels, Mn(IV) can be reduced both chemically and bacterially to the Mn(II) oxidation state (Jaudon et al., 1989). MMT has been found to be persistent in natural aquatic and soil environments in the absence of sunlight, with a tendency to sorb to soil and sediment particles (Garrison et al., 1995). In the presence of light, photodegradation of MMT is rapid, with identified products including a manganese carbonyl that readily oxidizes to manganese tetroxide (Garrison et al., 1995).

Manganese is often transported in rivers adsorbed to suspended sediments. Most of the manganese from industrial sources found in a South American river was bound to suspended particles (Malm et al., 1988). The tendency of soluble manganese compounds to adsorb to soils and sediments can be highly variable, depending mainly on the cation exchange capacity and the organic composition of the soil (Hemstock & Low, 1953; Schnitzer, 1969; McBride, 1979; Curtin et al., 1980; Baes & Sharp, 1983; Kabata-Pendias & Pendias, 1984). The oxidation state of manganese in soils and sediments can be altered by microbial activity (Geering et al., 1969; Francis, 1985).

Manganese in water can be significantly bioconcentrated at lower trophic levels. Bioconcentration factors (BCFs) of 10 000–20 000 for marine and freshwater plants, 2500–6300 for phytoplankton, 300–5500 for marine algae, 800–830 for intertidal mussels, and 35–930 for fish have been estimated (Folsom et al., 1963; Thompson et al., 1972). The high reported BCFs probably reflect the essentiality of manganese for a wide variety of organisms; specific uptake mechanisms exist for essential elements.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Concentrations of manganese in seawater reportedly range from 0.4 to 10 ：g/litre (US EPA, 1984). In the North Sea, the northeast Atlantic Ocean, the English Channel, and the Indian Ocean, manganese content was reported to range from 0.03 to 4.0 ：g/litre. Levels found in coastal waters of the Irish Sea and in the North Sea off the coast of the United Kingdom ranged from 0.2 to 25.5 ：g/litre (Alessio & Lucchini, 1996). In a number of cases, higher levels in water (in excess of 1000 ：g/litre) have been detected at US hazardous waste sites, suggesting that, in some instances, wastes from industrial sources can lead to significant contamination of water (ATSDR, 1996).

In a 1974–1981 survey of 286 US river water samples, concentrations of dissolved manganese ranged from less than 11 ：g/litre (25th percentile) to more than 51 ：g/litre (75th percentile) (Smith et al., 1987), with a median of 24 ：g/litre. Mean groundwater concentrations were 20 and 90 ：g/litre from two geological zones in California (Deverel & Millard, 1988). The surface waters of Welsh rivers were reported to contain from 0.8 to 28 ：g manganese/litre. Concentrations of manganese ranged from 1 to 530 ：g/litre in 37 rivers in the United Kingdom and in the Rhine and the Maas and their tributaries (Alessio & Lucchini, 1996).

Concentrations of manganese in surface water are usually reported as dissolved manganese. Total manganese might be a better indicator, because manganese adsorbed to suspended solids can exceed dissolved manganese in many systems, and the bioavailability of manganese in this form has not been established (NAS, 1977; US EPA, 1984).

Natural ("background") levels of manganese in soil range from 40 to 900 mg/kg, with an estimated mean of 330 mg/kg (Cooper, 1984; US EPA, 1985a; Schroeder et al., 1987; Eckel & Langley, 1988; Rope et al., 1988). Accumulation of manganese in soil usually occurs in the subsoil and not on the soil surface (WHO, 1981).

According to a National Research Council of Canada report (Stokes et al., 1988), manganese concentrations in air tend to be lowest in remote locations (about 0.5–14 ng/m^3 on average), higher in rural areas (40 ng/m^3 on average), and still higher in urban areas (about 65–166 ng/m^3 on average) (see Table 2). Similar concentrations have been reported elsewhere, leading to the conclusion that annual manganese concentrations

Table 2: Average levels of manganese in air.

a) Atmospheric air (worldwide)[a]:

Type of location	Average concentration (ng/m³)	Range (ng/m³)
Remote		
Continental	3.4	<0.18–9.30
Oceanic	14.2	0.02–79
Polar	0.5	0.01–1.5
Rural	40	6.5–199
Urban		
Canada	65	20.0–270
USA	93	5.0–390
Europe	166	23.0–850
Other	149	10.0–590

b) US ambient air[b]:

Type of location	Concentration (ng/m³)		
	1953–1957	1965–1967	1982
Nonurban	60	12	5
Urban	110	73	33
Source dominated	No data	250–8300	130–140

[a] Adapted from Stokes et al. (1988).
[b] Adapted from US EPA (1984).

average 10–30 ng/m^3 in areas far from known sources and 10–70 ng/m^3 in urban and rural areas without major point sources of manganese (WHO, 1999). Manganese concentrations in air tend to be highest in source-dominated areas (e.g., those with foundries), where values can reach 8000 ng/m^3 (US EPA, 1984; Stokes et al., 1988). Annual averages of manganese concentrations in air near foundries may rise to 200–300 ng/m^3 and to over 500 ng/m^3 in air near ferro- and silicomanganese industries (WHO, 1999).

Manganese concentrations in air have been measured in many specific locations. In the Vancouver, Canada, area, for example, annual geometric mean concentrations of manganese ranged from <10 to 30 ng/m^3 in 1984 (Stokes et al., 1988). Over the period of 1981–1992, Loranger & Zayed (1994) found average manganese concentrations in Montreal, Canada, of 20 and 60 ng/m^3 in areas of low and high traffic density, respectively. More recently, Loranger & Zayed (1997) found the average concentration of total manganese in an urban site in Montreal to be 27 ng/m^3. In selected periods in the 1970s, annual mean concentrations of manganese were reported to range from 3 to 16 ng/m^3 in two German cities, from 42 to 455 ng/m^3 in Belgium, and from 20 to 800 ng/m^3 in Japanese cities (WHO, 1999).

As Table 2 shows, manganese concentrations in air in the USA have decreased over the past three decades (Kleinman et al., 1980; US EPA, 1984), a trend believed to be due primarily to the installation of industrial emission controls (US EPA, 1984, 1985b). In Ontario, Canada, as well, annual average manganese concentrations in air have decreased along with total suspended particulate levels (Stokes et al., 1988).

6.2 Human exposure

The most significant source of manganese exposure for the general population is food (Table 3). A summary of mean manganese concentrations in 234 foods analysed by the US Food and Drug Administration is presented in Table 4. Although wide ranges of manganese concentrations in foods have been reported, the highest manganese concentrations are found in nuts (up to 47 ：g/g) and grains (up to 41 ：g/g). Lower levels are found in milk products (0.02–0.49), meat, poultry, fish, and eggs (0.10–3.99 ：g/g), and fruits (0.20–10.38 ：g/g). Tea and leafy green vegetables have also been found to be dietary sources of manganese (Davis et al., 1992). The US concentrations given in Table 4 are generally similar to concentrations reported from other countries. For example, during a 1992 survey conducted by Canada's Department of Fisheries and Oceans, manganese was detected in muscle samples from bluefin tuna (*Thunnus thynnus*) (Hellou et al., 1992); concentrations in 14 samples ranged from 0.16 to 0.31 ：g/g dry weight, with a mean of 0.22 ：g/g.

Although manganese is considered an essential element, a Recommended Daily Allowance (RDA) has not been established in the USA because of insufficient data (NRC, 1989). However, the Food and Nutrition Board of the US National Research Council establishes Estimated Safe and Adequate Daily Dietary Intake (ESADDI) levels when data are insufficient to establish an RDA. These levels generally parallel amounts of the compound usually delivered via the diet, although some individuals consume greater or smaller amounts. The ESADDI levels for manganese are 0.3–0.6 mg/day for infants up to 6 months old, 0.6–1.0 mg/day for infants 6 months to 1 year old, 1.0–1.5 mg/day for children 1–3 years old, 1.0–2.0 mg/day for children 4–10 years old, and 2.0–5.0 mg/day for people over 10 years old (NRC, 1989).

Table 3 presents an example of manganese intake from foodstuffs based on estimated dietary patterns in the USA. Manganese intake among individuals varies greatly, however, depending upon dietary habits. For example, an average cup of tea contains 0.4–1.3 mg manganese, so individuals consuming three cups of tea per day can receive negligible amounts of manganese or up to 4 mg daily from this source alone (Schroeder et al., 1966; Pennington et al., 1986). Thus, some

Table 3: Summary of typical human exposure to manganese.[a]

	Exposure medium		
Parameter	**Water**	**Air**	**Food**
Typical concentration in medium	4 μg/litre	0.023 μg/m³	1.28 μg/calorie
Assumed daily intake of medium by 70-kg adult	2 litres	20 m³	3000 calories
Estimated average daily intake by 70-kg adult	8 μg	0.46 μg[b]	3800 μg
Assumed absorption fraction	0.03[c]	1[c]	0.03[d]
Approximate absorbed dose	0.24 μg	0.46 μg	114 μg

[a] Adapted from US EPA (1984); [b] Assumes 100% deposition in the lungs; [c] No data; assumed value; [d] Davidsson et al. (1988).

persons consume more or less than the estimated daily intakes noted above (NAS, 1980; Pennington et al., 1986; Davis et al., 1992). Indeed, estimates of daily intake for adults in the USA range from 2.0 to 8.8 mg (NAS, 1977; Patterson et al., 1984; US EPA, 1984; WHO, 1984; Pennington et al., 1986).

Although gastrointestinal absorption of manganese is only 3–5% (Mena et al., 1969; Davidsson et al., 1988) (see section 7), food is not only the largest source of manganese exposure in the general population, but also the primary source of absorbed manganese (Table 3). The bioavailability of manganese from vegetable sources is substantially decreased by dietary components such as fibre and phytates (US EPA, 1993). Individuals with iron deficiency exhibit increased rates of manganese absorption (Mena et al., 1969, 1974).

In 1962, the public drinking-water supplies in 100 large cities in the USA were surveyed, and 97% contained less than 100 μg manganese/litre (Durfor & Becker, 1964). A 1969 survey of 969 systems reported that 91% contained less than 50 μg/litre, with a mean concentration of 22 μg/litre (ATSDR, 1996). In the Federal Republic of Germany, mean concentrations of manganese in drinking-water were reported to range from 1 to 63 μg/litre (Alessio & Lucchini, 1996).

Certain groups are more highly exposed to manganese than the general population. Infants given prepared infant foods and formulas, for example, may be more highly exposed to manganese than adults in the general population. Collipp et al. (1983) reported that concentrations of manganese in infant formulas range from 34 to 1000 μg/litre, compared with concentrations of 10 μg/litre in human milk and 30 μg/litre in cow's milk; Lavi et al. (1989) found an even lower concentration of manganese in market milk (16 ± 2 μg/litre), suggesting that the difference between formula and milk could be even greater in some regions. Because of the high manganese levels in prepared infant foods and formulas, some infants might ingest more than the ESADDI for their age group (Pennington et al., 1986; NRC, 1989).

Table 4: Manganese concentrations in selected foods.[a]

Type of food	**Range of mean concentrations (ppm; μg/g or mg/litre)**
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

[a] Adapted from Pennington et al. (1986).

In addition, people living in the vicinity of ferromanganese or iron and steel manufacturing facilities, coal-fired power plants, or hazardous waste sites can be exposed to elevated manganese particulate matter in air, although this exposure is likely to be much lower than in the workplace. Loranger & Zayed (1997) estimated average exposure doses of respirable manganese and total manganese in an urban site (botanical gardens) in Montreal, Canada, to be 0.005 and 0.008 μg/kg body weight per day (0.35 and 0.56 μg/day for a 70-kg person), respectively. Similarly, the daily intake of manganese in the air by the general US population was estimated to be less than 2 μg (WHO, 1981). According to a study by Pellizari et al. (1992) and subsequent analyses by the US EPA (1994a, 1994b), measurements of personal exposure levels in an urban area in the USA (Riverside, California) in 1990 indicated that about half the population had 24-h personal exposures to PM_{10} (particulate matter with an aerodynamic diameter less than or equal to 10 μm) manganese above 0.035 μg/m³ (0.7 μg/day, assuming a ventilation rate of 20 m³/day), while the highest 1% of the population had exposures above 0.223 μg/m³ (4.46 μg/day). By contrast, intakes in areas of the USA with ferro- or silicomanganese industries were as high as 10 μg/day, with 24-h peak values exceeding 100 μg/day (WHO, 1981).

People living in regions of natural manganese ore deposits or where manganese-containing materials (e.g., pesticides, batteries) are used or disposed of can also be exposed to elevated levels of manganese in soil or water. For example, Kawamura et al. (1941) reported on six Japanese families exposed to high levels (at least 14 mg/litre) of manganese in their drinking-water; the contamination was believed to result from manganese that leached from batteries buried near the well. Children are especially likely to receive elevated doses from manganese-containing soils because they have a higher intake of soil (mainly through hand-to-mouth contact) than adults (Calabrese et al., 1989). Organomanganese compounds such as MMT can be absorbed through the skin (Tanaka, 1994).

In the workplace, exposure to manganese is most likely to occur by inhalation of manganese fumes or manganese-containing dusts. These dusts can contain various manganese oxides as well as manganese in the oxides of other elements, such as potassium permanganate, manganese ferric oxide ($MnFe_2O_4$), and manganese silicate ($MnSiO_3$) (Pflaumbaum et al., 1990). Exposure is a concern mainly in the ferromanganese, iron and steel, dry-cell battery, and welding industries (WHO, 1986). Exposure can also occur during manganese mining and ore processing, and dermal exposure and inhalation can occur during the application of manganese-containing fungicides.

Manganese air concentrations of 1.5–450 mg/m^3 have been reported in US manganese mines (US EPA, 1984), 0.30–20 mg/m^3 in ferroalloy production facilities (Saric et al., 1977), 0.02–5 mg/m^3 in German foundries (Coenen et al., 1989), 1–4 mg/m^3 during welding with electrodes (Sjögren et al., 1990), up to 14 mg/m^3 during welding with welding wire (Pflaumbaum et al., 1990), and 3–18 mg/m^3 in a dry-cell battery facility (Emara et al., 1971). Many of the more recent studies on occupational exposures to manganese have recorded average exposure levels of 1 mg manganese/m^3 or less in the workplace (Roels et al., 1987, 1992; Mergler et al., 1994; Lucchini et al., 1995). Thus, for workers in industries using manganese, the major route of exposure might be inhalation from workplace air rather than ingestion of food.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Manganese absorption occurs primarily from the gastrointestinal tract after ingestion and from the alveolar lining after inhalation of manganese-containing dust or fumes. Several studies in animals indicate that key determinants of absorption are the absorption pathway and the specific compound in which manganese is present (Smith et al., 1995; Roels et al., 1997). Roels et al. (1997) studied manganese levels in the blood and brain tissue of rats exposed to repeated doses of manganese chloride or manganese dioxide administered by oral gavage, intraperitoneal injection, or intratracheal instillation. Manganese chloride was readily absorbed after administration by each of these routes and distributed in brain tissue to varying degrees. Manganese dioxide, on the other hand, was significantly absorbed and distributed in the brain to varying degrees when administered by intraperitoneal injection and intratracheal instillation, but not when administered orally. Higher levels of manganese in tissue were found after administering manganese chloride by intratracheal instillation compared with manganese dioxide. The authors concluded that the route of exposure might be a critical determinant of how absorbed manganese is distributed in the brain. In addition, when manganese dioxide was administered by either intratracheal instillation or oral gavage, manganese levels in the blood rose and fell more slowly than when manganese chloride was given, indicating a marked difference in the absorption kinetics of these two manganese compounds. The finding that the body handles manganese dioxide more slowly than manganese chloride suggests that manganese dioxide might remain in the body longer, contributing longer to body burden, albeit at much lower levels. Whether this is true and whether this indicates greater toxicological risk in cases of prolonged low-level exposure to manganese dioxide are unclear.

A second study also found that route of exposure affects absorption of manganese. Tjälve et al. (1996) found that intranasal instillation of manganese (Mn^{2+}) in rats resulted in initial uptake of manganese in the olfactory bulbs of the brain, whereas intraperitoneal administration resulted in low uptake in the olfactory bulbs. The authors suggested that olfactory neurons might serve as a pathway for manganese uptake and distribution to the brain (bypassing the blood–brain barrier) during intranasal exposure.

Another key determinant of absorption appears to be dietary iron intake, with low iron levels leading to increased manganese absorption (Mena et al., 1969). In addition, several studies in animals indicate that gastrointestinal absorption of manganese might vary with age (Rehnberg et al., 1980, 1981).

The amount of manganese absorbed across the gastrointestinal tract in humans varies, but typically averages about 3–5% (Mena et al., 1969; Davidsson et al., 1988). Particles that are deposited in the lower airways are probably absorbed, whereas particles depos-

ited in the upper airways are generally swallowed via mucociliary clearance; thus, they can be absorbed from the gastrointestinal tract as well.

Regardless of manganese intake, adult humans generally maintain stable tissue levels of manganese through a homeostatic mechanism regulating the excretion of excess manganese (US EPA, 1984). The major route of manganese excretion is via the bile, although some excretion occurs in urine, milk, and sweat (US EPA, 1993).

Limited data suggest that manganese can undergo changes in oxidation state within the body. Support for this hypothesis comes from the observation that the oxidation state of the manganese ion in several enzymes appears to be Mn(III) (Utter, 1976; Leach & Lilburn, 1978), whereas most manganese intake from the environment is as Mn(II) or Mn(IV). The rate and extent of manganese reduction/oxidation reactions might be important determinants of manganese retention in the body.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Lung inflammation has been reported following single inhalation exposures to 2.8–43 mg/m^3 for manganese dioxide or manganese tetroxide particulates in rodent species (Bergstrom, 1977; Adkins et al., 1980; Shiotsuka, 1984). It is important to note that an inflammatory response of this type is not unique to manganese-containing particles, but is characteristic of nearly all inhalable particulate matter (US EPA, 1985b). Thus, it might not be manganese alone that causes the inflammatory response from single exposures, but possibly the particulate matter itself.

Following single oral exposures, LD_{50}s ranged from 275 to 804 mg/kg body weight per day for manganese chloride in different rat strains (Holbrook et al., 1975; Kostial et al., 1989; Singh & Junnarkar, 1991). Reported LD_{50}s from single exposures to manganese sulfate and manganese acetate in rats were 782 and 1082 mg/kg body weight per day, respectively (Smyth et al., 1969; Singh & Junnarkar, 1991).

8.2 Irritation and sensitization

Little information is available on the irritant and contact sensitivity properties of manganese compounds. Manganese salts failed to induce lymph node cell proliferation in the murine local lymph node assay, a predictive test for the detection of contact allergens (Ikarashi et al., 1992). The manganese-containing fungicide maneb has been reported to be a sensitizer in animal tests, but little information exists on whether this effect occurs in humans (Thomas et al., 1990). Contact sensitization in humans has been reported in one study (see section 9.2).

8.3 Short-term exposure

Results from studies of short-term exposures in experimental animals indicate that the lungs and nervous system are the major target organs following the inhalation of manganese compounds. For example, Maigetter et al. (1976) found increased susceptibility to pneumonia in mice exposed via inhalation to 69 mg manganese/m^3 as manganese dioxide for 3 h/day for 1–4 days. Effects on the nervous system associated with short-term exposure to manganese compounds are presented in section 8.7.

8.4 Long-term exposure

8.4.1 Subchronic exposure

Results from studies of subchronic exposures in experimental animals also indicate that the lungs and nervous system are the major target organs following the inhalation of manganese compounds. Signs of lung inflammation have been reported in rhesus monkeys exposed via inhalation to 0.7 mg manganese/m^3 as manganese dioxide for 22 h/day over 10 months (Suzuki et al., 1978). Effects on the nervous system associated with subchronic exposure to manganese compounds are presented in section 8.7.

Systemic effects reported following subchronic oral exposures to manganese compounds include changes in blood cell counts (leukocytes, erythrocytes, neutrophils), reduced liver weight, and decreased body weight (Gray & Laskey, 1980; Komura & Sakamoto, 1991; NTP, 1993). In mice fed 284 mg manganese/kg body weight per day for 100 days, for example, red blood cell count was decreased by manganese acetate and manganese chloride; white blood cell count was decreased by manganese acetate, manganese chloride, and manganese dioxide; and haematocrit was decreased by manganese carbonate ($MnCO_3$) (Komura & Sakamoto, 1991).

8.4.2 Chronic exposure and carcinogenicity

Available data from animal studies involving oral exposure to manganese as well as from epidemiological studies involving inhalation exposure to manganese suggest that similar chronic toxicities (i.e., neurological effects) occur regardless of the valence state of the

inorganic manganese compounds (e.g., manganese dioxide, manganese tetroxide). In experimental animals, the nervous system is the major organ affected following long-term oral and inhalation exposure to manganese. These data are described in more detail in section 8.7. Few chronic inhalation exposure studies in animals are available, and these studies reported effects in the nervous system. Significant effects in other organ systems following long-term exposure to manganese have not been reported. Available data from animal studies suggest that it is unlikely that other significant effects result from long-term oral exposure to manganese (NTP, 1993).

Information on the carcinogenic potential of manganese is limited, and the results are difficult to interpret with certainty. For example, male rats exposed to up to 331 mg manganese/kg body weight per day (as manganese sulfate) for 2 years had an increased incidence of pancreatic cell adenomas (3/50, 4/51, and 2/51 in the low, mid, and high dose groups); this type of tumour was noted in only one female in the mid dose group. The investigators indicated that these lesions, although low in incidence, were "a concern" and attributed to manganese treatment because pancreatic cell hyperplasia was observed in all treatment groups, although neither hyperplasia nor adenomas were observed in controls of either sex (Hejtmancik et al., 1987a). On the other hand, a small increase in the incidence of pituitary adenomas was noted in female mice at 905 mg manganese/kg body weight per day (as manganese sulfate), but not in males at 722 mg manganese/kg body weight per day. The incidence was considered equivocal because lesions had been observed in previous studies as well as in historical controls (Hejtmancik et al., 1987b). In a 2-year study, no evidence of cancer was noted in male and female F344 rats given 20–200 and 23–232 mg manganese sulfate/kg body weight per day, respectively, via feed (NTP, 1993). A marginally increased incidence of thyroid gland follicular cell adenomas was observed in male and female $B6C3F_1$ mice given 52–585 and 65–731 mg manganese sulfate/kg body weight per day, respectively, in the feed for 2 years (NTP, 1993). Intraperitoneal injection of mice with manganese sulfate (20 weeks) led to an increased incidence of lung tumours (Stoner et al., 1976), but intramuscular injection of rats and mice with manganese or manganese dioxide did not result in tumours (Furst, 1978). Firm conclusions on the carcinogenic potential of manganese cannot be made based on the equivocal carcinogenicity data reported for rodents and the paucity of evidence from other species.

8.5 Genotoxicity and related end-points

Manganese sulfate was not mutagenic to *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 in either the presence or absence of S9 from Aroclor 1254-induced liver from rats or Syrian hamsters in studies performed at two different laboratories (Mortelmans et al., 1986), but it was reported elsewhere to be genotoxic to strain TA97 (Pagano & Zeiger, 1992). Manganese chloride was not mutagenic in *S. typhimurium* strains TA98, TA100, and TA1535, but it was mutagenic in TA1537, and conflicting results were obtained for TA102 (Wong, 1988; De Méo et al., 1991). A fungal gene conversion/reverse mutation assay in *Saccharomyces cerevisiae* strain D7 indicated that manganese sulfate was mutagenic (Singh, 1984).

Manganese chloride produced gene mutations *in vitro* in a mouse lymphoma assay (Oberly et al., 1982). It also caused DNA damage in human lymphocytes when tested *in vitro* using the single-cell gel assay technique in the absence of metabolic activation, but it caused no DNA damage when S9 was present (De Méo et al., 1991). The results of an *in vitro* assay using Chinese hamster ovary (CHO) cells showed that manganese sulfate induced sister chromatid exchange in both the presence and absence of S9 from Aroclor 1254-induced rat liver (Galloway et al., 1987). In a separate assay, manganese sulfate also induced chromosomal aberrations in CHO cells in the absence of S9 but not in its presence (Galloway et al., 1987). In contrast, manganese chloride was not clastogenic when tested *in vitro* in the absence of metabolic activation using FM3A cells (Umeda & Nishimura, 1979), although it did cause chromosomal aberrations in the root tips of *Vicia faba* (Glass, 1955, 1956). Potassium permanganate caused chromosomal aberrations in FM3A cells (Umeda & Nishimura, 1979) but not in a primary culture of cells from Syrian hamster embryos (Tsuda & Kato, 1977) when tested in the absence of metabolic activation. Magnesium chloride caused cell transformation in Syrian hamster embryo cells (Casto et al., 1979).

Manganese chloride did not produce somatic mutations in *Drosophila melanogaster* fruit flies (Rasmuson, 1985). Manganese sulfate did not induce sex-linked recessive lethal mutations in the germ cells of male *D. melanogaster* (Valencia et al., 1985).

In vivo assays in mice showed that oral doses of manganese sulfate or potassium permanganate caused micronuclei and chromosomal aberrations in bone marrow (Joardar & Sharma, 1990). In contrast, oral doses of manganese chloride did not cause chromosomal aberrations in the bone marrow or spermatogonia of rats (Dikshith & Chandra, 1978).

The results of *in vitro* studies show that at least some chemical forms of manganese have mutagenic potential. However, as the results of *in vivo* studies in mammals are inconsistent, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds.

8.6 Reproductive and developmental toxicity

Considerable information is available on the reproductive and developmental effects of manganese in animals. Mice exposed subcutaneously to 0, 2, 4, 8, or 16 mg manganese chloride tetrahydrate/kg body weight per day on gestation days 6–15 showed no treatment-related effects on the number of total implants, early resorptions, dead fetuses, or sex ratio. However, a significant increase in the number of late resorptions was found in the 4, 8, and 16 mg/kg body weight per day groups. Significant maternal toxicity was associated with the 8 and 16 mg/kg body weight per day groups (Sánchez et al., 1993). A single intratracheal dose of 160 mg manganese/kg (as manganese dioxide) in rabbits caused slow degenerative changes in the seminiferous tubules and led to sterility (Seth et al., 1973; Chandra et al., 1975). Abnormal sperm morphology was observed in mice treated with 23–198 mg manganese/kg body weight per day as potassium permanganate or manganese sulfate by gavage in water for up to 3 weeks (Joardar & Sharma, 1990). No gross or histopathological lesions or organ weight changes were observed in the reproductive organs of rodents exposed to 1300 mg manganese/kg body weight per day for 14 days or fed up to 1950 mg manganese/kg body weight per day for 13 weeks (NTP, 1993). From the available evidence, no firm conclusions on effects in male reproductive organs can be made, and reproductive performance was not evaluated in many of these studies.

A slight decrease in pregnancy rate was observed in female rats exposed to 130 mg manganese/kg body weight per day as manganese tetroxide in the diet for 90–100 days before breeding (Laskey et al., 1982). Female reproductive parameters such as litter size, ovulations, resorptions, or fetal weights were not affected in rats consuming excess manganese as manganese tetroxide in feed or water (Laskey et al., 1982; Kontur & Fechter, 1985), except at concentrations so high (1240 mg/kg body weight per day) that water intake by the dams was severely reduced. In mice, inhalation exposure of females to 85 mg manganese/m^3 (as manganese dioxide) for 16 weeks prior to conception and 17 days after conception led to a decrease in average pup weight at birth and decreased activity levels (Lown et al., 1984). Webster & Valois (1987) found that intraperitoneal injection of pregnant mice with 12.5 mg manganese/kg body weight (as manganese sulfate) on days 8–10 of gestation resulted in exencephaly and embryolethality. Finally, manganese chloride administered by gavage at doses of 0, 25, 50, or 75 mg/kg body weight per day caused major dose-dependent abnormalities in the fetuses when administered to gestating rats for the duration of gestation, but did not cause major abnormalities in the fetuses when administered to pregnant rabbits during the period of organogenesis (Szakmáry et al., 1995).

In a rat teratology study, intravenous injection of 20 μmol manganese chloride/kg body weight (1.1 mg manganese/kg body weight) on days 6–17 of pregnancy induced mild skeletal malformations in the fetuses; the no-observed-adverse-effect level (NOAEL) was 0.28 mg manganese/kg body weight (Treinen et al., 1995). Similar effects were observed in another study (Grant & Ege, 1995) when administration was by injection, but not when manganese was administered by gavage at 400 μmol manganese chloride/kg body weight (22 mg manganese/kg body weight). These results suggest that parenteral administration has a much greater potential for developmental toxicity than oral exposure.

In rabbits exposed to manganese by intratracheal instillation, a single dose of 160 mg manganese/kg body weight (as manganese dioxide) resulted in a slow degeneration of the seminiferous tubules over a period of 1–8 months. This was associated with loss of spermatogenesis and complete infertility (Seth et al., 1973; Chandra et al., 1975). Similar degenerative changes in testes have been observed in rats and mice following intraperitoneal injection of manganese sulfate (Singh et al., 1974; Chandra et al., 1975) and in rabbits following intravenous injection of manganese chloride (Imam & Chandra, 1975).

8.7 Immunological and neurological effects

As with exposure to other airborne particulate matter, an increased susceptibility to infection has been observed in mice and guinea-pigs exposed to manganese via inhalation for a short period (Maigetter et al., 1976; Adkins et al., 1980). Altered blood levels of leukocytes, lymphocytes, and neutrophils have been observed in rats and mice that ingested manganese in the feed for short-term (33 mg/kg body weight per day for 14 days) or subchronic (284 mg/kg body weight per day for 100 days) durations (Komura & Sakamoto, 1991; NTP, 1993). However, it is unknown if these changes are associated with any significant impairment of the immune system.

No evidence of neurological effects was seen in rhesus monkeys (0.01–1.1 mg manganese tetroxide/m^3) or macaque monkeys (20–40 mg manganese chloride/m^3) exposed to manganese via inhalation over subchronic and chronic periods (Ulrich et al., 1979). However, intravenous administration of 5–40 mg manganese/kg (as manganese chloride) to cebus monkeys did result in movement tremors accompanied by increased manganese in the globus pallidus and substantia nigra regions of the brain (Newland & Weiss, 1992).

Decreased levels of dopamine were found in several regions of the brain (caudate and globus pallidus) in rhesus monkeys exposed to 30 mg manganese/m^3 (as manganese dioxide) via inhalation for 2 years (Bird et al., 1984).

A decrease in pup retrieval behaviour was observed in maternal mice exposed to 61 mg manganese/m^3 (as manganese dioxide) via inhalation for 18 weeks (Lown et al., 1984). In another study, Morganti et al. (1985) observed moderate changes in open-field behaviour in mice exposed to 72 mg manganese/m^3 (as manganese dioxide) for 18 weeks.

In general, effects from inhalation exposure to manganese in experimental animals occur at levels higher (30–70 mg manganese/m^3) than those at which effects have been reported in humans (0.14–1 mg total manganese dust/m^3 for preclinical neurological alterations and 2–22 mg total manganese dust/m^3 for overt neurological disease). This evidence suggests that laboratory animals, especially rodents, might not be as sensitive as humans, and possibly other primates, to the neurological effects of inhalation exposure to manganese.

There are substantial data on neurological effects in animals following ingestion of manganese. In one study, decreases in spontaneous activity, alertness, touch response, muscle tone, and respiration were observed in mice dosed once by oral gavage with 58 mg manganese/kg body weight (as manganese chloride) (Singh & Junnarkar, 1991). Rats developed a rigid and unsteady gait after 2–3 weeks of exposure to a higher level (150 mg/kg body weight per day) of manganese chloride (Kristensson et al., 1986).

Mice ingesting food containing manganese chloride, manganese acetate, manganese carbonate, or manganese dioxide (284 mg/kg body weight per day) for 100 days or manganese tetroxide (137 mg/kg body weight per day) for 90 days showed significantly decreased motor activity (Gray & Laskey, 1980; Komura & Sakamoto, 1991). Two of the third-generation mice exhibited staggered gait and histochemical changes after drinking water containing manganese chloride (10.6 mg/kg body weight per day) over three generations (Ishizuka et al., 1991). Conversely, rats showed increased activity and aggression when exposed to 140 mg manganese chloride/kg body weight per day in drinking-water for 4 weeks (Chandra, 1983) and just increased activity when exposed to 40 mg manganese chloride/kg body weight per day for 65 weeks (Nachtman et al., 1986).

Numerous studies have reported alterations in brain neurotransmitter levels and function, brain histochemistry, or neuronal enzyme function. These neurochemical changes have been observed in rats and mice following ingestion of manganese (as manganese chloride) administered via the feed, drinking-water, or gavage (in water) at doses ranging from 1 to 2270 mg manganese/kg body weight over intermediate exposure periods (i.e., 14–364 days) (Bonilla, 1978; Chandra & Shukla, 1978; Deskin et al., 1980; Gianutsos & Murray, 1982; Chandra, 1983; Bonilla & Prasad, 1984; Ali et al., 1985; Eriksson et al., 1987; Subhash & Padmashree, 1991). Similar alterations were reported after chronic exposures (>365 days) to 275 mg manganese dioxide/kg body weight in the feed of mice (Komura & Sakamoto, 1992) or 40 mg manganese chloride/kg body weight in drinking-water of rats (Lai et al., 1984).

Neurochemical alterations have also been reported in rats following intraperitoneal injection of manganese at doses ranging from 2.2 to 4.4 mg manganese chloride/kg body weight over intermediate exposure periods (Sitaramayya et al., 1974; Shukla et al., 1980; Seth et al., 1981). Decreased neurotransmitter receptor binding was observed in macaca monkeys following subcutaneous injection of manganese dioxide at 38 mg/kg body weight for 26 months (Eriksson et al., 1992). Changes in region-specific neuronal populations were reported in rats receiving manganese chloride from their drinking-water for either 4 or 8 weeks (Sarhan et al., 1986). The actual manganese dose administered over the total experimental period was not reported by the authors. However, daily intakes of at least 10.7 mg manganese/kg body weight are estimated based on initial average body weight and water intake reported in the study.

Neurobiochemical changes have been detected in neonate rats at doses similar to or slightly above dietary levels (1–10 mg manganese/kg body weight per day for 24–60 days, as manganese chloride) (Chandra & Shukla, 1978; Deskin et al., 1980), which could indicate that young animals may be more susceptible to manganese than adults. Oner & Senturk (1995) demonstrated that manganese induces learning deficits in rats dosed with 357 ：g manganese/kg body weight for 15 or 30 days; these effects were reversible.

9. EFFECTS ON HUMANS

A requirement for manganese in humans was determined based on symptoms observed in a subject inadvertently fed a diet deficient in manganese for 3.5 months (Doisy, 1972). It has been determined that manganese is needed for the functioning of key enzymes that play a role in cellular protection from damaging free radical species, maintenance of healthy skin, and synthesis of cholesterol (Freeland-Graves et al., 1987;

Friedman et al., 1987). Based upon case-studies in people with low blood manganese and known requirements in animals, it is thought that manganese may also play a role in bone mineralization, metabolism of proteins, lipids, and carbohydrates, energy production, metabolic regulation, and nervous system functioning (Schroeder et al., 1966; Freeland-Graves et al., 1987; Hurley & Keen, 1987; Freeland-Graves & Llanes, 1994; Wedler, 1994). However, the link between inadequate manganese nutrition and its role in these body functions in humans requires further investigation.

Manganism is a progressive, disabling neurological syndrome that typically begins with relatively mild symptoms and evolves to include dull affect, altered gait, fine tremor, and sometimes psychiatric disturbances. Because some of these symptoms resemble those of Parkinson's disease, many investigators have used terms such as "Parkinsonism-like disease" and "manganese-induced Parkinsonism" to describe symptoms observed with manganese poisoning. Although symptoms of manganism resemble those of Parkinson's disease, significant differences have been noted. In terms of clinical presentation, Barbeau (1984) noted that the hypokinesia and tremor present in patients suffering from manganism differed from those seen in Parkinson's disease. Drawing from the literature, Calne et al. (1994) noted other features that can also distinguish manganism from Parkinson's disease; psychiatric disturbances early in the disease (in some cases), the "cock walk" (see below), a propensity to fall backward when displaced, less frequent resting tremor, more frequent dystonia, and failure to respond to dopaminomimetics (at least in the late stages of the disease) were characteristic of manganism. Beuter et al. (1994) showed that 10 manganese-exposed workers (average exposure of 13.9 years; average blood manganese level of 1.06 ∶g/dl) and 11 patients with Parkinsonism were significantly different from the controls (n = 11) in functional asymmetries between right and left hand. Therefore, use of terms such as "Parkinsonism-like disease" and "manganese-induced Parkinsonism" are somewhat misleading. Nonetheless, the use of these terms may help health providers and health surveillance workers recognize the effects of manganese poisoning when encountering it for the first time in occupational or environmental settings. These terms appear in the discussion below when they were used by study authors in their reports (shown in italics). The term "manganism" is used as well.

Long-term exposures to manganese in occupational settings can result in a progressive neurological dysfunction, which can produce a disabling syndrome referred to as manganism. Mergler & Baldwin (1997) have described this disease progression as a "slow deterioration of well-being which can be initially detected as early neurofunctional alterations... [among exposed groups], later on, as sub-clinical signs in individuals... and finally as a full blown neurological disease — manganism." Progression along this continuum is thought to be a function of the dose and duration of exposure, as well as individual susceptibilities. In general, the clinical effects of high-level inhalation exposure to manganese do not become apparent until exposure has occurred for several years, but some individuals begin to show signs of neurological alterations after as little as 1–3 months of exposure (Rodier, 1955).

Pathological findings in manganism and Parkinson's disease also differ. In humans with chronic manganese poisoning, lesions are more diffuse, found mainly in the pallidum, the caudate nucleus, the putamen, and even the cortex. In people with Parkinson's disease, lesions are found in the substantia nigra and other pigmented areas of the brain (Barbeau, 1984). Moreover, Lewy bodies are usually not found in substantia nigra in cases of manganism, but are almost always found in cases of Parkinson's disease (Calne et al., 1994). Magnetic resonance imaging of the brain reveals accumulation of manganese in cases of manganism, but little or no changes in people with Parkinson's disease; fluorodopa positron emission tomography scans are normal in cases of manganism, but abnormal in people with Parkinson's disease (Calne et al., 1994).

The first signs of manganism are usually subjective and non-specific, often involving generalized feelings of weakness, heaviness or stiffness of the legs, anorexia, muscle pain, nervousness, irritability, and headache (Rodier, 1955; Whitlock et al., 1966; Mena et al., 1967; Tanaka & Lieben, 1969; Sjögren et al., 1996). These signs are frequently accompanied by apathy and dullness, along with impotence and loss of libido; especially in the case of miners, more extreme manifestations of psychomotor excitement, such as aggressive or destructive behaviour, emotional lability, and bizarre compulsive activities, are also associated with the first stages of manganism (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967; Emara et al., 1971; Abdel-Hamid et al., 1990; Wennberg et al., 1991; Chu et al., 1995).

More specific clinical signs of basal ganglia dysfunction characterize the next stage and can include a slow or halting speech without tone or inflection, a dull and emotionless facial expression, slow and clumsy movement of the limbs or altered gait, late motor deficits, and fine tremor (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967; Tanaka & Lieben, 1969; Smyth et al., 1973; Yamada et al., 1986; Ky et al., 1992; Wennberg et al., 1992; Hochberg et al., 1996; Mergler & Baldwin, 1997).

As the disease progresses, walking becomes difficult and a characteristic staggering gait develops, the "cock walk," in which patients strut on their toes, with elbows flexed and the spine erect (Calne et al., 1994). Muscles become hypertonic, and voluntary movements can be accompanied by fine tremor (Chu et al., 1995; Mergler & Baldwin, 1997). In some cases, psychological disturbances (manganese mania, manganese psychosis) precede or accompany the final stages of disease (Rodier, 1955; Mena et al., 1967; Cook et al., 1974; Mergler & Baldwin, 1997). Few data are available regarding the reversibility of these effects; they are thought to be largely irreversible. Some evidence indicates that recovery can occur when exposure ceases (Smyth et al., 1973). Manganism has been documented in welders and in workers exposed to high levels of manganese dust or fumes in mines or foundries.

The studies cited above describe overt manganism resulting from long-term inhalation exposures to 2–22 mg total manganese dust/m^3 (Schuler et al., 1957; Whitlock et al., 1966; Tanaka & Lieben, 1969; Cook et al., 1974; Saric et al., 1977; Huang et al., 1989). Evidence from recent occupational exposure studies (described below) suggests that early or preclinical signs of neurological effects can occur in generally asymptomatic workers exposed to much lower levels of manganese (about 0.14–1 mg total manganese dust/m^3) for several years (Roels et al., 1987, 1992; Iregren, 1990; Chia et al., 1993; Mergler et al., 1994; Lucchini et al., 1995). However, the reported values are only estimates of actual exposure levels. Often, time-weighted averages of workplace exposures are reported, and dose–response relationships cannot be determined. In addition, exposures are generally reported as total manganese dust or the respirable fraction of total dust, which can be defined differently across studies (e.g., PM_5 [particulate matter with an aerodynamic diameter less than or equal to 5 ∶m] or PM_{10}).

9.1 Case reports

Whitlock et al. (1966) reported a case-study of two workers exposed to manganese-containing fumes (3.5 mg manganese/m^3 average; no data on exact compounds) from an electric arc used to cut and cleave manganese castings. Symptoms of ataxia, weakness, and decreased mental ability developed about 9–12 months following exposure. These symptoms improved after the patients were treated with ethylenediaminetetraacetic acid (EDTA). Rosenstock et al. (1971) reported a case of a male who developed classic symptoms of manganism after 14 months of exposure to manganese (dose unknown) from the fumes and dust of a steel foundry. After being unable to work for 3 years, the patient was treated with 6–12 g levodopa/day, with the largest dose providing improvement in facial expression, speech, and muscle tone. Six men exposed to manganese (22 mg manganese/m^3) for an unspecified period at an ore crushing plant developed signs including somnolence, abnormal gait, slurred speech, ataxia, masklike faces, and bradykinesia. Treatment with 8 g levodopa/day did not alleviate the neurological effects observed in these workers (Cook et al., 1974).

An outbreak of a disease with manganism-like symptoms was reported in a group of six Japanese families (about 25 people) exposed to high levels of manganese in their drinking-water (Kawamura et al., 1941). Symptoms included a masklike face, muscle rigidity and tremors, and mental disturbance. Five people, all elderly, were severely affected (2 died), 2 were moderately affected, 8 were mildly affected, and 10 (all children or young adults) were not affected. These effects were postulated to be due to the contamination of well-water with manganese (14 mg/litre) that leached from batteries buried near the well. Manganese concentrations decreased over time, so the original level of manganese was probably higher than 14 mg/litre. This case has been interpreted as an indication that the elderly may be more sensitive than younger people to the toxic effects of manganese (Davis & Elias, 1996).

A man noticed weakness and impaired mental capacity after mistakenly ingesting low doses of potassium permanganate (1.8 mg/kg) instead of potassium iodide for several weeks to treat lung congestion (Holzgraefe et al., 1986). Although exposure was stopped after 4 weeks, *a syndrome similar to Parkinson's disease* developed after about 9 months. In another case, five patients given manganese parenterally for an average of 6 years showed early neurological symptoms of poisoning, while four others, exposed for an average of 4 years, did not (Mirowitz et al., 1991). In a child, accidental ingestion of potassium permanganate (174 mg/kg) resulted in severe local corrosion of the mouth, oesophagus, and stomach, but there was no evidence of systemic toxicity (Southwood et al., 1987).

There are few reports regarding dermal exposure to manganese in humans. In most cases, manganese uptake across intact skin is expected to be very limited. However, effects and elevated urinary manganese levels were observed in a man burned with a hot acid solution containing 6% manganese (Laitung & Mercer, 1983). There are also reports of workers experiencing effects from dermal exposure to organic manganese compounds. Headache and paraesthesia were among the symptoms reported in workers exposed dermally to MMT after a spill (doses unknown; Tanaka, 1994). Two young Brazilian agricultural workers developed *Parkinsonian syndrome* (Ferraz et al., 1988) and a 37-year-old Italian man developed *Parkinsonism* (Meco et al., 1994) after chronic dermal and inhalation exposure to the fungicide maneb.

9.2 Epidemiological studies

The lungs, nervous system, and reproductive system are the main organs affected following inhalation exposures to manganese, although other effects have also been observed. For example, in a study of 126 enamellers and 64 decorators from five factories in the ceramics industry, Motolese et al. (1993) found that 48 workers were sensitized to at least one substance; positive sensitization test results with manganese dioxide were found in only 2 of the workers, however. The remainder of this section focuses on the effects more commonly reported in epidemiological studies — lung, nervous system, and reproductive system effects.

Inhalation of particulate manganese compounds such as manganese dioxide and manganese tetroxide leads to an inflammatory response in human lungs. Symptoms and signs of lung irritation and injury can include cough, bronchitis, pneumonitis, and reductions in lung function (Lloyd Davies, 1946; Roels et al., 1987; Abdel-Hamid et al., 1990; Akbar-Khanzadeh, 1993).

Pneumonia has been reported to result from both acute and long-term inhalation exposure to manganese dioxide dusts (Lloyd Davies, 1946; Tanaka, 1994). These effects have been noted mainly in people exposed to manganese dust under occupational conditions, although respiratory effects have also occurred in residential populations (WHO, 1987). A higher incidence of pneumonia and a higher rate of deaths from pneumonia compared with the general population were observed among residents exposed to manganese dust from a ferromanganese factory as well as among the factory workers (WHO, 1987; Tanaka, 1994). However, a threshold level for respiratory effects has not been established. The increased susceptibility to respiratory infection might be secondary to the lung irritation and inflammation caused by inhaled particulate matter rather than caused by the manganese alone. It is likely that the inflammatory response begins shortly after exposure and continues for the duration of the exposure.

Although available studies are not adequate to define the dose–response curve or determine whether there is a threshold for neurotoxicity, the lowest level of exposure to manganese dust at which neurological effects occur was reported by Iregren (1990) and Wennberg et al. (1991). These investigators compared 30 male workers exposed to manganese for 1–35 years during employment at two Swedish foundries with an unexposed control group of 60 workers (matched by age, type of work, and geographical area) using eight tests from the Swedish Performance Evaluation System and two additional manual tests. The mean and median levels of manganese in the foundry air were measured at 0.25 and 0.14 mg/m^3, respectively, and available data indicated that these levels had been consistent over the past 17–18 years. The exposed workers exhibited significantly inferior performance in simple reaction time, digit span, and finger tapping. When a secondary match was performed, with scores on verbal tests used as an additional matching criterion (which reduced the size of the reference group to 30), the same test differences remained, although the difference was not significant for the digit span test. Although the subjects did not exhibit the signs of clinical manganism described above, these changes were indicators of manganese-induced neurological effects (Iregren, 1990; Wennberg et al., 1991).

The study results reported by Iregren (1990) and Wennberg et al. (1991) are supported by evidence presented by Roels et al. (1987, 1992) and Chia et al. (1993, 1995). Roels et al. (1992) detected early neurological effects in male workers at an alkaline battery plant exposed to manganese dusts (manganese dioxide). Compared with 101 male workers without industrial exposure, the 92 exposed workers showed significantly poorer eye–hand coordination, hand steadiness, and visual reaction time. A Lifetime Integrated Exposure, for both respirable and total manganese dust, was estimated for each of the exposed workers (expressed as exposure in mg manganese/m^3 multiplied by the number of years of exposure, or mg/m^3 × year). Based on an analysis of the data by a logistic regression model, it was suggested that there was an increased risk of peripheral tremor at a Lifetime Integrated Exposure level of 3.575 mg/m^3 × year total manganese dust or 0.73 mg/m^3 × year respirable (PM_5) dust; dividing by an exposure duration of 5.3 years, these values are equivalent to 0.67 mg/m^3 and 0.14 mg/m^3 for total manganese dust and respirable manganese dust, respectively. This total manganese dust exposure level (0.67 mg/m^3) is slightly higher than the median found to be associated with effects in the 1990 Iregren and the 1991 Wennberg et al. studies (0.14 mg/m^3). The Lifetime Integrated Exposure at which an increased risk of abnormal neurofunction occurs is based on exposures in an occupational setting and might be biased because of the "healthy worker effect" (i.e., the most susceptible individuals were not incorporated into the study).

The Chia et al. (1993) study also reported neurological deficits in an occupational cohort of 17 manganese "baggers" in Singapore who were administered the WHO Neurobehavioural Core Test Battery, as well as several supplementary tests and a subjective questionnaire (with questions on 37 symptoms related to the nervous system) taken from the Operational Guide to the Neurobehavioural Core Test Battery. The exposed workers had significantly poorer motor speed, visual-motor coordination, visual scanning, visual-motor and response speed, and visual-motor coordination and steadiness than a control group. Twenty of the 37 symptoms in the questionnaire were also reported more frequently by the exposed workers than by the control

group, although the differences were significant only for insomnia and profuse sweating. The mean manganese level in air (from 1981 to 1991) in the factories was reported to be 1.59 μg/litre (1.59 mg/m^3; 8-hour time-weighted average). Chia et al. (1995) conducted another study with a larger group of exposed workers (32 subjects exposed to the same mean level of manganese in air reported above), focusing in more detail on postural stability; the exposed workers exhibited significantly poorer postural stability compared with a control group.

A study by Mergler et al. (1994) also supports the findings of Iregren (1990), Wennberg et al. (1991), Roels et al. (1987, 1992), and Chia et al. (1993, 1995). This epidemiological study included 74 male workers from a ferromanganese and silicomanganese alloy factory, matched with 74 referents from a pool of 145 non-occupationally exposed men residing in the vicinity. Environmental levels of total manganese dust at the factory were measured at 0.014–11.48 mg/m^3 (median 0.151 mg/m^3; mean 1.186 mg/m^3), whereas manganese levels in respirable dust (PM_{10} samples) ranged from 0.001 to 1.27 mg/m^3 (median 0.032 mg/m^3; mean 0.122 mg/m^3). The authors noted that exposures at the factory were known to have been much higher in the recent past. The mean duration of exposure was 16.7 years. The manganese-exposed workers showed decreased performance on tests of motor function, and they exhibited lower levels of cognitive flexibility, difficulty in set shifting, and lower olfactory perception thresholds. This is the first study to report the latter effect (lower olfactory perception threshold). The workers also displayed significantly greater anger, tension, fatigue, and confusion as determined by the Profile of Mood States test.

A study by Lucchini et al. (1995) also found evidence of neurobehavioural effects at exposure levels comparable to those reported above. During a period of forced cessation from work, 58 clinically asymptomatic workers exposed to manganese dust for periods of 1–28 years (mean 13 years) were tested for simple reaction time, finger tapping, digit span, additions, symbol digit, and shapes comparison. Geometric mean concentrations of manganese in total dust were measured in different work areas and ranged from 70–1590 μg/m^3 (10 years before the study was undertaken) to 27–270 μg/m^3 (at the time of the study). A Cumulative Exposure Index was calculated for each subject. It took into account the type of job(s) the subject performed at the plant, the average annual airborne manganese concentration in respirable dust characteristic of the job(s), and the duration of employment in the job(s). The authors found correlations between the Cumulative Exposure Index and performance on the finger tapping, symbol digit, digit span, and additions tests; higher indices were associated with poorer performance. In addition, the authors found correlations between manganese levels in blood and urine of the workers and performance (the higher the blood and urine levels, the poorer the performance) when the levels were measured after exposure ended. This study is significant in that it is the first to demonstrate an association between biomarkers of exposure/body burden and the occurrence of neurological effects.

Impotence and loss of libido are common symptoms in male workers afflicted with clinically identifiable signs of manganism attributed to occupational exposure to manganese for 1–21 years (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967; Emara et al., 1971). These effects could lead to reduced reproductive success in men. Impaired fertility (measured as a decreased number of children per married couple) has been observed in male workers exposed for 1–19 years to manganese dust at levels (0.97 mg/m^3) that did not produce frank manganism (Lauwerys et al., 1985). In another study, Gennart et al. (1992) did not find an effect of manganese exposure (0.71 mg/m^3 for 6.2 years on average) on fertility. Impaired sexual function in men might be one of the earliest clinical manifestations of manganism; however, because dose–response information is unavailable, it is not possible to define a threshold for this effect. No information was found regarding reproductive effects in women.

Although most effects have been seen following chronic inhalation exposure to manganese in occupational settings, some epidemiological studies have reported adverse effects from ingestion of excess manganese in the environment. A manganism-like neurological syndrome was observed in an aboriginal population living on an island near Australia where environmental levels of manganese are high (Kilburn, 1987). Exposure levels were not provided, but the authors noted that manganese intake could occur not only through the oral route (food, water, soil), but also by inhaling manganese-containing dusts in the air (Cawte et al., 1987). Although manganese exposure was probably an etiologic factor, genetic factors, dietary deficiencies in antioxidants and calcium, and excess alcohol consumption could also have contributed to the neurological effects (Cawte et al., 1989).

More recently, Kondakis et al. (1989) reported that chronic intake of drinking-water containing elevated levels of manganese (1.8–2.3 mg/litre) led to an increased prevalence of neurological signs in elderly residents (average age 67 years) of two small towns in Greece. The effects were compared with those in similarly aged residents in two other communities where manganese levels were within ambient range (0.004 and 0.0015 mg/litre). The findings suggested that above-average oral exposure to manganese might be of health concern. However, although the comparison populations were reportedly very similar to each other, differences in

age, occupational exposures, or general health status could have accounted for the small differences observed. Similarly, Goldsmith et al. (1990) investigated a cluster of Parkinson's disease in southern Israel. The authors suggested that excess levels of aluminum, iron, and manganese in the drinking-water and the use of agricultural chemicals, including maneb and paraquat, in the area were common environmental factors that may have contributed to the observed cluster. However, the observed symptoms could not be conclusively attributed to manganese poisoning alone. By contrast, a recent study by Vieregge et al. (1995) on the neurological impacts of chronic oral intake of manganese in well-water found no significant differences between exposed and control populations in northern Germany. A group of 41 subjects exposed to 0.300–160 mg manganese/litre in well-water was compared with a control group of 71 subjects (matched for age, sex, nutritional habits, and drug intake) exposed to a maximum manganese concentration in well-water of 0.050 mg/litre. Neurological assessments revealed no significant difference between the two groups. Although the effects reported by Kondakis et al. (1989) and Goldsmith et al. (1990) are consistent with the known toxicological effects of manganese, the findings are inconclusive and are contradicted by the results of Vieregge et al. (1995). As a result, no firm conclusions on manganese-induced neurological effects in humans from chronic oral intake of manganese in drinking-water can be made at this time.

One report partially attributed neurological effects to chronic oral intake of manganese in food. Iwami et al. (1994), studying metal content in food and drinking-water in an area with a high rate of motor neuron disease (as determined from death certificates) compared with control areas, concluded that a high manganese content in food and a low *magnesium* content in drinking-water together explained the high incidence of motor neuron disease. The manganese content per 1800-kcal diet averaged 6.20 mg for local rice eaters and 3.83–4.67 mg in the control areas.

Several studies have reported an association between chronic exposure to maneb and neurological symptoms, but the effects could not be conclusively attributed to maneb alone. Ruijten et al. (1994) investigated the effects of chronic exposure to mixed pesticides (including zineb and maneb) on peripheral and autonomic nerve function using a previously exposed group of 131 Dutch bulb farmers and a control group of 67. The findings suggested exposure-related decreases in both autonomic and peripheral nerve function. Ferraz et al. (1988) reported the results of a questionnaire and neurological examination administered to 50 rural workers in Brazil who had had close contact with maneb (preparation and/or fumigation) for at least 6 months. Compared with a control group, the exposed group had a significantly higher prevalence of plastic rigidity with cogwheel phenomenon (neurological examination), as well as headache, fatigue, nervousness, memory complaints, and sleepiness (questionnaire). In both studies, however, the subjects were exposed to other substances, so the effects could not be definitively attributed to maneb. Meco et al. (1994) reported that *Parkinsonism* developed in a patient 2 years after chronic exposure to maneb had been discontinued. Initial symptoms observed were generalized bradykinesia, rigidity, and mild tremor associated with paraesthesias in the right leg, which subsequently spread to the right arm. Over a 3-year period, the tremor worsened and spread to the left limbs as well. Exposure levels were not defined in these studies.

10. EFFECTS EVALUATION

10.1 Evaluation of health effects

10.1.1 Hazard identification and dose–response assessment

Manganism, manganic pneumonia, and male reproductive effects (decreased libido, impotence, and decreased fertility) have been documented following chronic inhalation of manganese-containing respirable dusts in occupational settings (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967; Emara et al., 1971; Lauwerys et al., 1985). More recent reports have shown subclinical changes in neurological performance at low occupational exposure levels (Roels et al., 1987, 1992; Iregren, 1990; Wennberg et al., 1991; Mergler et al., 1994; Lucchini et al., 1995); it should be noted that even these low occupational exposure levels were at least three orders of magnitude higher than manganese levels in areas without industrial sources of manganese. A dose–response curve has not been well defined, but early signs of nervous system toxicity and overt manganism have been observed after inhalation exposure to total manganese dust levels that range from 0.14 to 1 mg/m^3 for the former and from 2 to 22 mg/m^3 for the latter. These neurological effects have been observed following exposure durations that span from 1 to 35 years (Schuler et al., 1957; Whitlock et al., 1966; Tanaka & Lieben, 1969; Cook et al., 1974; Saric et al., 1977; Roels et al., 1987, 1992; Iregren, 1990; Wennberg et al., 1991; Chia et al., 1993, 1995; Mergler et al., 1994; Lucchini et al., 1995). Estimated levels of inhalation exposure to manganese compounds have been reported as manganese in either total dust particles or the respirable fraction, based on particle size.

Although inconclusive, limited case reports and epidemiological studies report neurological effects associated with ingesting water (or other media) contain-

ing elevated manganese (Kawamura et al., 1941; Kilburn, 1987; Kondakis et al., 1989; Goldsmith et al., 1990; Iwami et al., 1994). Reports on neurological effects following exposure to pesticides containing manganese are similarly inconclusive (Ferraz et al., 1988; Ruijten et al., 1994).

Some evidence suggests that the elderly might be more sensitive than younger people to manganese (Davis & Elias, 1996). In addition, owing to various predisposing factors, certain other individuals might be more susceptible to adverse effects from exposure to excess manganese. These might include people with lung disease, people who are exposed to other lung irritants, neonates, individuals with iron deficiency, and people with liver disease.

Available data suggest that neurological effects can occur following chronic inhalation exposures in humans and intermediate and chronic oral exposures in animals to different manganese compounds. Manganese-induced neurological effects have been reported at lower airborne manganese concentrations in humans than in animals (Bird et al., 1984; Newland & Weiss, 1992). These data suggest that animal models, particularly rodent species, might be less useful for defining quantitative dose–response relationships, but helpful in elucidating the mechanism(s) for these effects. The basis for the difference in susceptibility across species is not yet understood and may be related to possible differences in the sensitivity of test methods used to detect neurobehavioural effects in animals compared with methods used to detect neurobehavioural effects in humans.

Little is known about the relative toxicity of different manganese compounds. Inhaled manganese compounds tend to produce more severe toxicity than ingested manganese compounds. This is probably attributable to the difference in route-specific uptake of manganese from the lung (often assumed at 100%) compared with the gastrointestinal tract (3–5%). Studies have shown that a greater proportion of a manganese dose appears in the blood and brain of rats exposed via inhalation or intranasal instillation than when the same dose is given orally (Tjälve et al., 1996; Roels et al., 1997).

10.1.2 Criteria for setting guidance values for manganese

There are several approaches to the development of a guidance value for manganese in air. A recently developed guidance value of 0.15 μg manganese/m^3 (WHO, 1999) is highlighted here as one example; other approaches are outlined in Appendix 4. The WHO (1999) guidance value was derived from the results of the study by Roels et al. (1992), which examined neurobehavioural end-points in 92 male workers exposed to manganese dioxide dust at an alkaline battery plant and 101 male workers without industrial manganese exposure. The manganese-exposed workers exhibited significantly poorer eye–hand coordination, hand steadiness, and visual reaction time. Sufficient data on participants' exposure levels and test performance were provided to enable development of a dose–response relationship and calculation of a benchmark dose. The lower 95% confidence limit of the benchmark dose (30 μg/m^3 for the 5% effect level) was used as an estimate of a NOAEL for neurological effects. The guidance value for manganese in air (WHO, 1999) was then derived as follows:

Guidance value = (30 μg/m^3 ÷ 50) × (5/7) × (8/24)

= 0.15 μg/m^3 (rounded value)

where:

- 30 μg/m^3 is the estimated NOAEL for neurological effects, calculated based on a benchmark dose analysis of results from a quality epidemiological study of workers exposed to manganese;
- 5/7 and 8/24 are factors used to convert intermittent exposure (5 days/week, 8 h/day) to continuous exposure; and
- 50 is the uncertainty factor (×10 for interindividual variation; ×5 for the potential for developmental effects in younger children). The uncertainty factor for developmental effects in younger children was obtained by analogy with lead, where neurobehavioural effects were found in younger children at blood lead levels five times lower than in adults; this finding was considered to be supported by evidence from studies in animals (WHO, 1999).

In considering development of a guidance value for oral intake of manganese, it must be noted that there is wide variability in human intake of manganese (from all sources) and that manganese is an essential nutrient for humans and animals. Daily manganese intake from food is estimated to be about 2–9 mg for adults, with an absorbed amount of about 100–450 μg/day based upon 5% gastrointestinal absorption (WHO, 1981). Some studies have reported that neurological effects may be related to ingestion of manganese in non-worker populations. However, these reports provide little information on the levels of ingested manganese that were associated with these effects. Although neurological effects might be a potential concern for people working or living at or near sites where ingestion or inhalation of high levels of manganese can occur (see section 9.2), no firm conclusion on a guidance value level for oral intake

of manganese other than estimated daily intake levels is considered possible.

10.1.3 Sample risk characterization

A theoretical estimate of inhalation exposures for the general population is presented based on available monitoring data on levels of manganese in air.

Table 2 shows estimates of the average levels of manganese in ambient air in remote, rural, and urban areas around the world (US EPA, 1984; Stokes et al., 1988). Using these data and a daily inhalation volume of 20 m^3 for a 70-kg adult, the average estimated daily intake of manganese from air in rural areas would be 0.8 μg/day, and this might increase to 1.3, 1.9, and 3.3 μg/day in urban areas in Canada, the USA, and Europe, respectively. In source-dominated areas with manganese-emitting industries or major foundry facilities, intake from air might rise to 4–6 μg/day (WHO, 1999). These estimates are based on the assumptions that there is 100% absorption of inhaled manganese and that an individual lives or works in these environments for a complete 24-h period. Thus, these exposure estimates could be further adjusted to reflect that fraction of a 24-h period during which a person is actually in any of these areas. For example, a person working for 8 h/day in an urban area of Canada, the USA, or Europe would be exposed to an adjusted estimate of 0.43–1.1 μg manganese during the workday (1.3–3.3 μg/day × 8/24). Consequently, for persons living or working in rural or urban environments, estimates of inhalation exposure would fall below or in the range of the reported guidance values for inhaled manganese. Appendix 4 includes examples of other guideline values reported for inhaled manganese. These values range from 0.8 μg/day (0.04 μg/m^3 × 20 m^3/day = 0.8 μg/day) up to an estimate of 3.0 μg inhaled manganese/day based on the guidance value described in section 10.1.2 (0.15 μg/m^3 × 20 m^3/day = 3.0 μg/day). It should be noted that the studies used in the risk assessment of inhaled manganese are occupational studies of adult male workers, and there is uncertainty about extrapolating the risk to women and children.

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

WHO (1981, 1986, 1987, 1999) has previously evaluated manganese, concluding that chronic manganese poisoning is a hazard in occupational settings. However, little information was available to assess the potential health risks in community exposure scenarios.

WHO has established a provisional guideline value of 0.5 mg/litre for manganese in drinking-water based on health (WHO, 1993), an annual air quality guideline of 0.15 μg/m^3 (WHO, 1999), and a workplace exposure limit in air of 0.3 mg/m^3 for respirable particles containing manganese (WHO, 1984, 1986, 1987, 1999).

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

12. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0174) reproduced in this document.

12.1 Human health hazards

Following long-term or repeated exposure to manganese, humans may present neurological and neuropsychiatric disorders known under the term manganism.

12.2 Advice to physicians

The psychiatric symptoms of manganese poisoning are transient. However, the neurological damage might be irreversible, although some patients have experienced partial regression of their symptoms after early removal from exposure (Mena et al., 1974).

Consequently, it is very important to remove from further exposure patients who present preclinical neurological disturbances or symptoms of manganism. Chelation therapy with, for example, EDTA might be effective in removing manganese from blood and tissues, but it has no permanent effect on symptomatic patients in the late stages of manganism (Bismuth et al., 1987; Dreisbach & Robertson, 1987; Ellenhorn & Barceloux, 1988; Tomes, 1997). Normal manganese levels are 2–8 μg/dl in blood and 0.1–0.8 μg/dl in urine. Plasma and urine manganese levels do not seem to correlate well with the severity of symptoms.

12.3 Health surveillance programme

The health surveillance programme of people exposed to manganese needs to include elements such as central nervous system disturbances (asthenia, anorexia, sleep problems, irritability, diminished libido).

13. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards can be found in the International Register of Potentially Toxic Chemicals (IRPTC), available from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

MANGANESE

0174
March 1995

CAS No: 7439-96-5
RTECS No: OO927500
UN No:
EC No:

Mn
Atomic mass: 54.9

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Dry sand, special powder.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting.	
EXPOSURE		**PREVENT DISPERSION OF DUST! AVOID EXPOSURE OF (PREGNANT) WOMEN!**	
Inhalation	Cough. Shortness of breath.	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin			
Eyes		Safety goggles or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Nausea.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers. Carefully collect remainder, then remove to safe place (extra personal protection: P2 filter respirator for harmful particles).	Symbol R: S:

EMERGENCY RESPONSE	STORAGE
	Separated from acids. Dry.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
GRAY-WHITE POWDER.

Physical Dangers
Dust explosion possible if in powder or granular form, mixed with air.

Chemical Dangers
Upon heating, toxic fumes are formed. Reacts violently with concentrated hydrogen peroxide. Reacts slowly with water more rapidly with steam and acids to produce flammable gas (hydrogen see - ICSC # 0001) causing fire and explosion hazard. Burns in nitrogen oxide above 200°C.

Occupational Exposure Limits
TLV: ppm; 0.2 mg/m^3 (ACGIH 1996).
MAK: ppm; 0.5 mg/m^3 (1994).

Routes of Exposure
The substance can be absorbed into the body by inhalation of its aerosol or fumes, and by ingestion.

Inhalation Risk
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

Effects of Short-term Exposure
Inhalation of dust may cause bronchitis and pneumonitis. The effects may be delayed.

Effects of Long-term or Repeated Exposure
The substance may have effects on the lungs and nervous system, resulting in bronchitis, pneumonitis, neurologic and neuropsychiatric disorders (manganism). Animal tests show that this substance possibly causes toxic effects upon human reproduction.

PHYSICAL PROPERTIES

Boiling point: 1962°C
Melting point: 1244°C
Relative density (water = 1): 7.2-7.4
Solubility in water: none

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. The recommendations on this Card also apply to ferro manganese.

ADDITIONAL INFORMATION

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APPENDIX 1 — SOURCE DOCUMENTS

Agency for Toxic Substances and Disease Registry (1996)

The *Toxicological profile for manganese (update)* (ATSDR, 1996) was prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) through a contract with the Research Triangle Institute. The updated profile was published as a draft for public comment in February 1998. Copies of the profile can be obtained from:

Division of Toxicology
Agency for Toxic Substances and Disease Registry
Public Health Service
US Department of Health and Human Services
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
USA

Dr M. Williams-Johnson, Division of Toxicology, ATSDR, and Dr S.G. Donkin, Dr S.W. Rhodes, and L. Kolb, Sciences International, Inc., Alexandria, Virginia, contributed to the development of the toxicological profile as chemical manager and authors. The profile has undergone three ATSDR internal reviews, including Green Border Review to assure consistency with ATSDR policy, a Health Effects Review, and a Minimal Risk Level Review. An external peer review panel was assembled for the update profile for manganese. The panel consisted of the following members: Dr J Greger, University of Wisconsin, Madison, Wisconsin; Dr D.J. Hodgson, University of Wyoming, Laramie, Wyoming; and Dr C. Newland, Auburn University, Auburn, Alabama. These experts collectively have knowledge of manganese's physical and chemical properties, toxicokinetics, key health end-points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the US *Comprehensive Environmental Response, Compensation, and Liability Act*, as amended.

Scientists from ATSDR reviewed the peer reviewers' comments and determined which comments were to be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record. The citation of the peer review panel should not be understood to imply its approval of the profile's final content.

Hazardous Substances Data Bank (1998)

Copies of the information on manganese stored in the Hazardous Substances Data Bank (HSDB) can be obtained from:

Specialized Information Services
National Library of Medicine
National Institutes of Health
Public Health Service
US Department of Health and Human Services
8600 Rockville Pike
Bethesda, Maryland 20894
USA

HSDB is peer reviewed by a scientific review panel composed of expert toxicologists and other scientists.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on manganese and its compounds was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

BHP Minerals, San Francisco, USA

Department of Health, London, United Kingdom

Department of Toxicology and Chemistry, National Institute for Working Life, Solna, Sweden

Environment Canada, Ottawa, Canada

Health Canada, Ottawa, Canada

Institute of Occupational Health, Helsinki, Finland

National Chemicals Inspectorate, Solna, Sweden

National Institute for Environmental Health and Safety, Washington, DC, USA

National Institute for Occupational Safety and Health, Atlanta, USA

National Institute for Public Health, Prague, Czech Republic

National Institute of Occupational Health, Budapest, Hungary

Public Health Centre of the Capital City, Prague, Czech Republic

United States Environmental Protection Agency, Washington, DC, USA

Université de Montréal, Montreal, Canada

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Berlin, Germany, 26–28 November 1997

Members

Dr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Mr R. Cary, Health Directorate, Health and Safety Executive, Bootle, United Kingdom

Dr S. Dobson, Institute of Terrestrial Ecology, Huntingdon, United Kingdom

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Mr J.R. Hickman, Health Protection Branch, Health Canada, Ottawa, Ontario, Canada

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

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Mrs B. Dinham,[1] The Pesticide Trust, London, United Kingdom

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Dr B. Hansen,[1] European Chemicals Bureau, European Commission, Ispra, Italy

Dr J. Heuer, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Mr T. Jacob,[1] DuPont, Washington, DC, USA

Ms L. Onyon, Environment Directorate, Organisation for Economic Co-operation and Development, Paris, France

Dr H.J. Weideli, Ciba Speciality Chemicals Inc., Basel, Switzerland (representing CEFIC, the European Chemical Industry Council)

Secretariat

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[1] Invited but unable to attend.

APPENDIX 4 — ADDITIONAL APPROACHES FOR GUIDANCE VALUE DEVELOPMENT

An additional approach in deriving an inhalation guidance value for manganese could involve dividing the exposed workers from the Roels et al. (1992) study into four quartiles to estimate a dose–response relationship and using the average cumulative exposure and average exposure duration for the lowest quartile of workers to calculate a NOAEL of 32 μg/m³ (adjusted for continuous exposure), which could be divided by an uncertainty factor of 300 (10 to account for human variability, 10 to account for less than lifetime exposure, and 3 to account for other weaknesses in the study and overall database — i.e., statistical weakness from only 23 people in each quartile, exposure to a manganese oxide other than manganese tetroxide, and a lack of reproductive data), yielding a guidance value of 0.1 μg/m³ (Egyed & Wood, 1996).

A guidance value might also be derived by using the geometric mean integrated respirable dust concentration reported in the Roels et al. (1992) study and adjusting for exposure duration to calculate an exposure-adjusted lowest-observed-adverse-effect level (LOAEL) of 50 μg/m³, which could be divided by an uncertainty factor of 1000 (10 to protect sensitive individuals, 10 to account for using a LOAEL instead of a NOAEL, and 10 to account for database limitations — extrapolation from subchronic to chronic exposure, inadequate reproductive and developmental data, and unknown differences in the toxicity of different forms of manganese), yielding a guidance value of 0.05 μg/m³ (US EPA, 1994b, 1994c; Davis, 1998). Other possible guideline values, calculated using other methods (e.g., benchmark, Bayesian, etc.), would range from 0.09 to 0.2 μg/m³ (US EPA, 1994a, 1994b, 1994c; Davis, 1998).

Alternatively, an inhalation guidance value could be derived based upon a LOAEL of 140 μg total manganese dust/m³ reported in the study by Iregren (1990), divided by an uncertainty/modifying factor of 900 (10 to account for use of a LOAEL instead of a NOAEL; 10 to account for human variability; and two modifying factors — 3 to account for effects from cumulative exposure to manganese, and 3 to account for potential differences in toxicity from different forms of manganese) and adjusted for continuous rather than intermittent exposure, yielding a provisional guidance value of 0.04 μg/m³ (ATSDR, 1996).

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au manganèse et à ses dérivés repose essentiellement sur un rapport intitulé *Toxicological profile for manganese (update), draft for public comment* et rédigé par l'Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services (ATSDR, 1996). On a également utilisé les informations contenues dans la Banque de données pour les substances dangereuses, une banque de données constituée et gérée par la National Library of Medicine, US Department of Health and Human Services (HSDB, 1998). Les dernières données sur lesquels s'appuient ces documents de base remontent à novembre 1998. Enfin, des données complémentaires ont été tirées des évaluations publiées par l'US Environmental Protection Agency (EPA) et l'Organisation mondiale de la Santé (OMS) ainsi que de divers autres documents. Les documents de base utilisés pour la rédaction de ce CICAD ne prennent pas en compte les effets du manganèse sur les écosystèmes. Aucune autre source documentaire (c'est-à-dire des documents rédigés par des organismes internationaux et soumis à une contrôle scientifique rigoureux) n'a pu être trouvée. Ce CICAD ne concerne donc que les effets que la présence de manganèse dans l'environnement peut avoir sur la santé humaine. On n'a pas cherché à déterminer les effets exercés sur les autres êtres vivants dans leur milieu naturel. On trouvera à l'appendice 1 des indications sur les sources documentaires utilisées. Les renseignements concernant l'examen du CICAD par des pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Berlin (Allemagne) du 26 au 28 novembre 1997. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC No 0174) établie par le Programme international sur la Sécurité chimique (IPCS, 1993) est également reproduite dans ce document.

Le manganèse (Mn) est un élément présent à l'état naturel dans les roches, le sol, l'eau et les aliments. Tous les êtres humains sont donc exposés au manganèse et ce dernier est un constituant naturel de l'organisme. La voie d'exposition la plus importante pour l'Homme est habituellement la voie alimentaire. Les doses journalières considérées comme suffisantes et sans danger vont de 1 à 5 mg de manganèse pour les enfants de 1 an et plus et les adultes. Elles correspondent généralement à l'apport d'origine alimentaire.

Le manganèse est libéré dans l'atmosphère principalement sous la forme de particules dont la destinée et le transport dépendent de leur taille et de leur densité ainsi que de la vitesse et de la direction du vent. Certains dérivés du manganèse sont très solubles dans l'eau, de sorte qu'on s'expose facilement à en ingérer une quantité importante en buvant de l'eau contaminée. Le manganèse présent dans l'eau peut subir une oxydation, s'adsorber sur les particules en suspension et sédimenter ensuite. Dans le sol, le manganèse peut migrer sous forme de particules dans l'air ou dans l'eau ou encore, s'il est présent sous la forme de composés solubles, en être éliminé par lessivage.

C'est chez les personnes employées dans des ateliers libérant des poussières à forte teneur en manganèse, ou qui vivent dans leur voisinage, que l'exposition au manganèse a le plus de chances d'être supérieure à la moyenne. Dans certaines régions, la population peut être exposée au manganèse libéré dans l'atmosphère par la combustion d'essence sans plomb additionnée d'un antidétonnant organomanganique, le méthylcyclopentadiénylmanganèse-tricarbonyle (MMT). Certaines personnes peuvent absorber une quantité excessive de manganèse en consommant l'eau de puits contaminés par du manganése provenant de piles ou de pesticides. De même les enfants peuvent se contaminer en portant à leur bouche de la terre contenant du manganèse en excès.

Le manganèse est un nutriment essentiel pour l'Homme. Il intervient dans la minéralisation des os, dans le métabolisme énergétique et dans celui des protéines, dans la régulation du métabolisme, dans la protection des cellules contre les radicaux libres et dans la formation de glycosaminoglycanes. L'inhalation ou l'ingestion de quantités excessives de manganèse peut toutefois avoir des effets indésirables. A dose administrée équivalente, on retrouve davantage de manganèse dans l'encéphale après inhalation qu'après ingestion et la plupart des effets qu'il provoque sont liés à une exposition chronique par la voie respiratoire. On sait peu de chose de la toxicité relative des divers composés du manganèse. Toutefois, les données disponibles indiquent que plusieurs d'entre eux sont capables de provoquer des effets neurologiques; on a observé ces effets chez l'Homme après exposition chronique (365 jours ou davantage) par la voie respiratoire ainsi que chez l'animal, après exposition de durée intermédiaire (15-364 jours) ou exposition chronique par voie buccale.

D'une manière générale, on constate, à la lumière des données disponibles, qu'une exposition à des concentrations excessives de manganèse pendant deux semaines ou moins (exposition brève) ou une période pouvant aller jusqu'à un an (exposition de durée intermédiaire) exerce un effet sur les voies respiratoires et sur le système nerveux, mais peu ou pas d'effets sur les autres organes. Une intoxication aiguë par inhalation de poussières à forte teneur en manganèse (en particulier sous forme de dioxyde MnO_2 ou de tétroxyde Mn_3O_4) peut provoquer une réaction inflammatoire au niveau pulmonaire qui, avec le temps, peut aboutir à une détérioration de la capacité fonctionnelle du poumon.

Cette toxicité pulmonaire se manifeste sous la forme d'une sensibilité accrue aux maladies infectieuses – bronchites par exemple – et peut évoluer vers une pneumopathie fibreuse. On a également observé une pneumopathie après une brève inhalation de particules contenant d'autres métaux. Cet effet pourrait donc être caractéristique d'une exposition à des particules par la voie respiratoire et ne pas être uniquement lié à la teneur de ces particules en manganèse.

Il existe quelques documents selon lesquels une exposition de durée intermédiaire à des dérivés du manganèse est susceptible d'exercer des effets sur le système nerveux central, mais on ne dispose pas d'estimation fiable du niveau d'exposition nécessaire pour produire de tels effets. Les études d'inhalation effectuées sur des animaux ont révélé l'existence d'effets biochimiques, respiratoires et neurocomportementaux. On n'a cependant pas déterminé quel était le seuil d'apparition de ces effets car le niveau d'exposition nécessaire à leur manifestation varie dans la proportion de 1 à 10.

En cas d'exposition chronique par la voie respiratoire, les principaux organes-cibles sont les poumons, le système nerveux et les gonades, encore que l'on ait également observé des effets au niveau d'autres organes. On a constaté des cas de pneumopathie fibreuse récidivante et des effets respiratoires aigus à la suite d'une exposition chronique au manganèse. Les effets sur le système nerveux se traduisent notamment par des troubles neurologiques et neuropsychiatriques pouvant aboutir à une pathologie de type parkinsonien connue sous le nom de manganisme. L'expérience incite à penser que les animaux de laboratoire, et notamment les rongeurs, ne sont pas aussi sensibles que l'Homme aux effets neurologiques provoqué par l'inhalation de manganèse. Au nombre des effets sur la fonction de reproduction figurent une réduction de la libido, l'impuissance et une diminution de la fécondité chez les sujets de sexe masculin. On ne dispose d'aucune information concernant les effets qui s'exerceraient sur la fonction génitale de la femme. L'expérimentation animale indique que le manganèse peut provoquer des lésions testiculaires et des résorptions tardives. Les données tirées de l'expérimentation animale et relatives aux effets de l'inhalation de manganèse sur le système immunitaire ou sur le développement foetal sont trop limitées pour que l'on puisse se prononcer véritablement au sujet de la signification de ces effets pour l'Homme.

On ne dispose que de données limitées sur le pouvoir cancérogène du manganèse et les résultats expérimentaux sont difficiles à interpréter de façon catégorique. L'administration chronique de sulfate de manganèse ($MnSO_4$) à des rats par la voie buccale a provoqué une légère augmentation des tumeurs du pancréas chez les mâles et un nombre un peu plus élevé d'adénomes hypophysaires chez les femelles. D'autres études portant sur le même composé n'ont pas mis de cancers en évidence chez le rat et une augmentation marginale de l'incidence des tumeurs affectant les cellules folliculaires de la thyroïde a été relevée chez des souris. D'après des études *in vitro,* il existe, chez certains composés tout au moins, un pouvoir mutagène. Quoi qu'il en soit, les études *in vivo* chez les mammifères donnent des résultats irréguliers et aucune conclusion générale ne peut en être tirée en ce qui concerne le risque génotoxique que pourrait comporter une exposition aux dérivés du manganèse.

Ingérés à forte dose par gavage, des sels concentrés de manganèse peuvent entraîner la mort des animaux, mais une exposition de brève durée par suite de la consommation d'aliments ou d'eau contaminés par du manganèse ne semble pas entraîner d'intoxication importante. De même, l'administration de sels de manganèse par la voie parentérale peut avoir un effet toxique sur le développement, mais ces effets ne s'observent pas après ingestion. On a décrit deux cas de neurotoxicité après ingestion, pendant une période de durée intermédiaire, de dérivés du manganèse par des sujets humains, mais les données sont trop limitées pour que l'on puisse définir le seuil de toxicité ou savoir si ces effets étaient imputables en totalité au manganèse. On possède quelques données sur les effets neurologiques ou autres, consécutifs, chez l'Homme, à l'ingestion prolongée de manganèse, mais les études dont elles sont tirées pêchent par l'incertitude qui entoure les voies d'exposition, les doses totales et l'existence d'autres facteurs de confusion. Les données fournies par les études sur l'Homme et l'animal sont insuffisantes pour permettre de déterminer les doses ou les effets à prendre en considération dans le cas d'une exposition de longue durée par la voie digestive. Les éléments dont on dispose au sujet des effets indésirables d'une ingestion prolongée de quantités excessives de manganèse sont évocateurs mais non concluants.

La voie percutanée ne semble pas devoir être prise sérieusement en considération et n'a d'ailleurs guère été étudiée. Les données dont on dispose se limitent à l'effet corrosif du permanganate de potassium ($KMnO_4$) ou à des cas d'absorption percutanée de dérivés organiques du manganèse comme le MMT.

A la lumière de ces données, il apparaît clairement qu'une exposition au manganèse sur les lieux de travail peut entraîner des effets neurologiques ou respiratoires. D'autres données, plus limitées, incitent également à penser que l'ingestion de manganèse en quantités excessives du fait de sa présence dans l'environnement peut aussi avoir des effets neurologiques indésirables. Certains individus peuvent être porteurs de facteurs qui les prédisposent à être plus vunérables aux effets indésirables d'une exposition à des quantités excessives de manganèse. Il peut s'agir notamment de malades atteints de pneumopathies, de personnes exposées à

d'autres irritants pulmonaires, de nouveau-nés, de personnes âgées, de sujets souffrant de carence martiale ou encore d'hépatiques.

Il y a plusieurs manières de parvenir à une valeur-guide pour le manganèse présent dans l'air. On peut citer ici à titre d'exemple le chiffre de 0,15 :g de manganèse par m^3 qui a été récemment proposé; on trouvera également d'autres méthodes envisageables pour obtenir ces valeurs-guides.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre el manganeso y sus compuestos se basa fundamentalmente en el informe titulado *Perfil toxicológico del manganeso (actualización), proyecto de información pública*, preparado por la Agencia para el Registro de Sustancias Tóxicas y Enfermedades, Departamento de Salud y Servicios Sociales de los Estados Unidos (ATSDR, 1996). Se utilizó asimismo la información contenida en el Banco de Datos de Sustancias Peligrosas, servicio que ha creado y mantiene la Biblioteca Nacional de Medicina del Departamento de Salud y Servicios Sociales de los Estados Unidos (HSDB, 1998). Se examinaron los datos identificados en estos documentos originales hasta noviembre 1998. Hay información adicional procedente de otras referencias, como las evaluaciones preparadas por la Agencia para la Protección del Medio Ambiente de los Estados Unidos (EPA) y la Organización Mundial de la Salud (OMS), así como de diversos informes publicados. Los documentos originales utilizados en la preparación del presente CICAD no comprenden los efectos del manganeso en el medio ambiente. No se identificaron otras fuentes (documentos preparados por una organización nacional y sujetos a un examen científico riguroso) sobre este tema. Por consiguiente, en este CICAD se abordan sólo los niveles en el medio ambiente como fuente de exposición humana. Tampoco se ha intentado evaluar en el presente documento los efectos sobre los organismos en el medio ambiente. La información sobre la disponibilidad de los documentos originales figura en el apéndice 1. La información acerca del examen colegiado de este CICAD se presenta en el apéndice 2. Su aprobación como evaluación internacional se realizó en una reunión de la Junta de Evaluación Final, celebrada en Berlín, Alemania, los días 26-28 de noviembre de 1997. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0174) para el manganeso, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El manganeso (Mn) es un elemento natural del medio ambiente, que se encuentra en las rocas, el suelo, el agua y los alimentos. Así pues, todas las personas están expuestas al manganeso y es un componente normal del organismo. La vía de exposición más importante para el ser humano suelen ser los alimentos. Se ha establecido una ingesta diaria inocua y suficiente de 1-5 mg de manganeso para niños de un año y mayores hasta la edad adulta; estos niveles generalmente se corresponden con las cantidades del compuesto que se reciben a través de los alimentos.

El manganeso se libera en el aire fundamentalmente como materia particulada, y el destino final y el transporte de las partículas dependen de su tamaño y densidad y de la velocidad y la dirección del viento. Algunos compuestos de manganeso son muy solubles en agua, de manera que se puede producir una exposición importante por el consumo de agua de bebida contaminada. El manganeso del agua superficial se puede oxidar o adsorber en las partículas del sedimento y depositarse en el fondo. El del suelo puede pasar como materia particulada al aire o al agua, y los compuestos solubles de manganeso pueden sufrir un proceso de lixiviación a partir del suelo.

Las exposiciones al manganeso mencionadas más arriba son más probables en el caso de las personas que trabajan o viven cerca de fábricas o de otros lugares donde se liberan cantidades significativas de polvo de manganeso en el aire. En algunas regiones, la población general puede estar expuesta al manganeso liberado en el aire por la combustión de la gasolina sin plomo que contiene el compuesto orgánico de manganeso, metil-ciclopentadienilo-manganeso tricarbonilo (MMT) como ingrediente antidetonante. Algunas personas pueden estar expuestas a un exceso de manganeso en el agua potable, por ejemplo cuando se filtra al agua de los pozos manganeso de las baterías o de plaguicidas. Los niños pueden estar expuestos a un exceso de manganeso en el suelo por la costumbre de llevarse las manos a la boca.

El manganeso es un nutriente esencial del ser humano que desempeña una función en la mineralización de los huesos, en el metabolismo proteico y energético, en la regulación metabólica, en la protección de las células del efecto perjudicial de sustancias con radicales libres nocivos y en la formación de glucosaminoglucanos. Sin embargo, la exposición a niveles elevados mediante inhalación o ingestión puede producir efectos adversos en la salud. Para dosis comparables, llega al cerebro más manganeso después de la inhalación que de la ingestión, y la mayor parte de los efectos en la salud están asociados con la exposición crónica por inhalación. Es poco lo que se sabe acerca de la toxicidad relativa de los distintos compuestos de manganeso. Sin embargo, hay pruebas que ponen de manifiesto que diversos compuestos de manganeso pueden inducir efectos neurológicos; estos efectos se han observado tras una exposición crónica por inhalación (365 días o más) en el ser humano y una exposición oral intermedia (15-364 días) y crónica en animales.

En general, los datos disponibles indican que la exposición a un exceso de manganeso durante 14 días o menos (aguda) o hasta un año (intermedia) tiene efectos en el sistema respiratorio y en el sistema nervioso, con un efecto escaso o nulo en otros órganos. La exposición aguda por inhalación a concentraciones elevadas de polvo de manganeso (en concreto de dióxido de manganeso [MnO_2] y de tetróxido de manganeso [Mn_3O_4]) puede provocar una respuesta inflamatoria en el pulmón,

que con el tiempo puede dar lugar a un trastorno de la función pulmonar. La toxicidad pulmonar se manifiesta en forma de una mayor susceptibilidad a infecciones como la bronquitis y puede producir neumonía mangánica. Se ha observado también neumonía tras exposiciones agudas por inhalación a partículas que contenían otros metales. Así pues, este efecto podría ser característico de la materia particulada inhalable y no depender solamente del contenido en manganeso de las partículas.

Hay un pequeño número de informes que parecen indicar que en la exposición intermedia a compuestos de manganeso por inhalación se producen efectos en el sistema nervioso central, pero no se dispone de estimaciones fidedignas sobre los niveles de exposición. Los estudios de inhalación en animales pusieron de manifiesto efectos bioquímicos, respiratorios y en el neurocomportamiento. Sin embargo, no se ha determinado un umbral para estos efectos, porque los niveles de exposición asociados con ellos varían en más de un orden de magnitud.

En la exposición crónica al manganeso por inhalación, los principales órganos afectados son los pulmones, el sistema nervioso y el sistema reproductor, aunque también se han observado efectos en otros sistemas de órganos. Este tipo de exposición se ha asociado con una neumonía mangánica recurrente y con efectos respiratorios agudos. Los efectos en el sistema nervioso incluyen síntomas neurológicos y neuropsiquiátricos que pueden culminar en una enfermedad semejante a la de Parkinson, conocida como manganismo; hay pruebas que indican que los animales de laboratorio, especialmente los roedores, no son tan sensibles como el ser humano, y posiblemente otros primates, a los efectos neurológicos provocados por la exposición al manganeso por inhalación. Los efectos reproductivos de la exposición crónica por inhalación son una reducción de la libido, impotencia y menor fecundidad en los hombres; no se dispone de información acerca de los efectos reproductivos en las mujeres. Los estudios realizados en animales indican que el manganeso puede producir daños directos en los testículos y resorciones tardías. Los datos obtenidos de estudios realizados con animales sobre los efectos del manganeso inhalado en el sistema inmunitario y en el desarrollo del feto son demasiado limitados para sacar conclusiones sobre la importancia de estos efectos en el ser humano.

La información sobre el potencial carcinogénico del manganeso es limitada y los resultados son difíciles de interpretar con certeza. Los estudios de exposición crónica por vía oral realizados con sulfato de manganeso ($MnSO_4$) en ratas pusieron de manifiesto un pequeño aumento en la incidencia de tumores pancreáticos en los machos y un ligero incremento de los adenomas de hipófisis en las hembras. En otros estudios realizados con sulfato de manganeso, no se observaron signos de cáncer en ratas y en ratones se detectó un aumento marginal de la incidencia de adenomas de las células foliculares de la glándula tiroides. Los resultados de los estudios *in vitro* ponen de manifiesto que por lo menos algunas formas químicas del manganeso tienen potencial mutagénico. Sin embargo, debido a las discrepancias entre los resultados de los estudios *in vivo* realizados en mamíferos, no se puede llegar a una conclusión general acerca del posible peligro genotóxico para el ser humano como consecuencia de la exposición a compuestos de manganeso.

La administración de dosis elevadas de sales concentradas de manganeso por vía oral mediante sonda puede provocar la muerte de los animales, pero no se ha observado que la exposición oral a través de los alimentos o del agua produzca una toxicidad significativa durante una exposición aguda o breve. Igualmente, la administración parenteral de sales de manganeso puede producir toxicidad en el desarrollo, pero no se encontraron efectos tras las exposición por vía oral. Se ha notificado que la exposición oral de duración intermedia del ser humano al manganeso produjo neurotoxicidad en dos casos, pero los datos son demasiado limitados para definir el umbral o juzgar si estos efectos se debieron completamente a la exposición al manganeso. Existen algunos datos acerca de los efectos neurológicos o de otro tipo para la salud de las personas debidos a la exposición oral crónica al manganeso, pero estos estudios están limitados por la incertidumbre en relación con las vías de exposición y los niveles de exposición total, así como por la existencia de otros factores de confusión. Los estudios en el ser humano y en animales no proporcionan información suficiente para determinar las dosis o los efectos que despiertan preocupación tras la exposición crónica por vía oral. Así pues, las pruebas disponibles para los efectos adversos asociados con la ingesta crónica de un exceso de manganeso son indicativas, pero no concluyentes.

La vía cutánea no parece revestir especial importancia y no se ha investigado en absoluto. Los datos disponibles se limitan a informes sobre los efectos corrosivos del permanganato potásico ($KMnO_4$) y a informes de casos de efectos debidos a la absorción cutánea de compuestos orgánicos del manganeso, como el MMT.

Según estos datos, es evidente que la exposición al manganeso puede producir efectos neurológicos y respiratorios adversos en el ámbito ocupacional. También hay pruebas limitadas que indican que los efectos neurológicos adversos pueden estar asociados con la ingesta de un exceso de manganeso en las condiciones del medio ambiente. Como consecuencia de los factores de predisposición, determinadas personas podrían ser más susceptibles a los efectos adversos de la exposición a un exceso de manganeso. Entre ellas

podrían estar las afectadas por enfermedades pulmonares, las expuestas a otras sustancias irritantes de los pulmones, los recién nacidos, los ancianos, y las personas con déficit de hierro o con enfermedades hepáticas.

Existen varios métodos para la obtención de un valor guía para el manganeso en el aire. Recientemente se ha obtenido un valor guía de 0,15 ìg de manganeso/m^3, que se destaca aquí como un posible ejemplo; también se han presentado algunos métodos adicionales.