Synthesis of scientific knowledge on the health risks following occupational exposure to manganese

STUDIES AND RESEARCH PROJECTS

Claude Ostiguy
Sylvain Malo
Paul Asselin

R-349

REPORT

irsst

Established in Québec since 1980, the Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) is a scientific research organization known for the quality of its work and the expertise of its personnel.

OUR RESEARCH *is working* for you!

MISSION

- To contribute, through research, to the prevention of industrial accidents and occupational diseases as well as to the rehabilitation of affected workers.
- To offer the laboratory services and expertise necessary for the activities of the public occupational health and safety prevention network.
- To disseminate knowledge, and to act as scientific benchmark and expert.

Funded by the Commission de la santé et de la sécurité du travail, the IRSST has a board of directors made up of an equal number of employer and worker representatives.

TO FIND OUT MORE...

Visit our Web site for complete up-to-date information about the IRSST. All our publications can be downloaded at no charge.
www.irsst.qc.ca

To obtain the latest information on the research carried out or funded by the IRSST, subscribe to *Prévention au travail*, the free magazine published jointly by the IRSST and the CSST.

Subscription: 1-817-221-7046

IRSST – Communications Division
505, boul. De Maisonneuve Ouest
Montréal (Québec)
H3A 3C2
Telephone: (514) 288-1551
Fax: (514) 288-7636
www.irsst.qc.ca

Synthesis of scientific knowledge on the health risks following occupational exposure to manganese

STUDIES AND RESEARCH PROJECTS

REPORT

Claude Ostiguy, Operations Division, IRSST
Sylvain Malo and Paul Asselin,
Commission de la santé et de la sécurité du travail

Cliquez recherche
www.irsst.qc.ca

This publication is available free of charge on the Web site.

This study was financed by the IRSST. The conclusions and recommendations are those of the authors.

SUMMARY

This report is a synthesis of current scientific knowledge based mainly on several critical reviews carried out by different international scientific experts and groups of experts as well as on some original articles. It responds to a request for information addressed to the IRSST by the CSST to document current knowledge on the main potential health effects on workers following occupational exposure to manganese (Mn), and particularly on the central nervous system.

Manganese is an essential trace element found in all living organisms and the level in the body is normally well controlled by the homeostatic process. It is found in low concentrations in soil, water, air and food, and everyone absorbs small daily doses that are weakly absorbed (3-5%) by the digestive system; this chronic absorption at low doses is considered as essential.

Occupational exposure may disturb the homeostatic balance and substantially increase the Mn concentration in the body, particularly if the absorption of the respirable fraction through the pulmonary pathway is very high. Mn then concentrates in the various target organs including certain parts of the brain where it will exert the most serious toxic effects. In fact, chronic occupational exposures by inhalation may lead to injury to the central nervous system (CNS), with the most serious effect being manganism, an occupational disease previously mistaken for Parkinson's disease. Reproductive effects, such as a reduction in fertility and impotence, have been observed in humans and animals. An increased incidence of bronchitis and altered pulmonary characteristics have also been documented following occupational exposures. Chemical pneumonias have also been noted in miners. These effects normally appear at concentrations above the CNS effects. The latency period for developing measurable effects on the CNS varies from a few months to more than 20 years and individual susceptibility seems to play an important role in it. Manganese is not currently considered a carcinogen.

Although clinical signs of manganism have rarely been reported at Mn concentrations below 5 mg/m^3 (current Québec standard for manganese and total dusts), several studies clearly show early signs of injury to the central nervous system at much lower exposure concentrations. In 2000, the American agency ATSDR established a concentration at which no effect (NOAEL) will occur on the CNS or pulmonary system. This level is 0.07 mg Mn/m^3 in respirable dust. Furthermore, epidemiological studies suggest that lifetime cumulative exposure is the best indicator, allowing correlation of occupational exposure with the early effects observed on the CNS. However, when neurological damage is measured, it is rarely reversible and tends to worsen over time, even in the absence of occupational exposure. As a result, it is important to intervene as rapidly as possible, in a phase that is possibly still reversible. A consensus seems to be developing in the scientific community on CNS injuries at a preclinical stage and on the irreversibility of certain effects. Along these lines, different organizations such as the American Conference of Governmental Industrial Hygienists, ACGIH, are currently considering lowering their recommendations. For the ACGIH, the value now considered would drop from 0.20 mg Mn/m^3 in total dusts to 0.030 mg Mn/m^3 in respirable dust (Intended change 2002).

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Manganese in the environment

Manganese (Mn, CAS number 7439-96-5) makes up approximately 0.10% of the earth's crust and is the 12th most abundant element (Francis & Forsyth 1995). It can be found in several oxidation states from -3 to +7, with the most common form in the environment being +4 (Keen and Leach 1988). Mn is found naturally in soil, river water, lake water and underground streams, in the ambient air as well as in food. We are all exposed to trace amounts in the air and consume it orally in food and water. Base levels are in the order of 0.004 ppm in water, 0.02 μg/m^{3*} in air, 40 to 900 ppm in soil (Cooper 1984; US EPA 1985a; Schroeder et al. 1987; Eckel & Langley 1988; Rope et al. 1988). The daily intake from food is in the order of 1 to 10 mg (ATSDR 2000, WHO 1997). Respiratory absorption is estimated at less than 2 μg/day (WHO 1981).

Manganese is considered a trace element essential for good health and is most frequently found in the +2 valence state in living organisms (Keen and Leach 1988; Stokinger 1981). The human body contains small amounts of Mn, and under normal conditions, our homeostatic system controls the quantities very well. The daily recommended dose is 2500 to 5000 μg with a gastrointestinal absorption rate in the order of 3 to 5% (ATSDR 2000).

Human activities can increase the manganese content in the environment, industrially or through the combustion of fossil fuels. In addition, the resuspension of soil containing Mn may contribute to the atmospheric concentration (EPA 1984a, 1985b, 1985c, 1987; Lioy 1983). The most important sources of environmental manganese related to industrial activity are ferroalloy production plants, iron and steel foundries, thermal power plants, coke ovens, and dusts from mining operations (EPA 1983, 1985b, 1985c; ATSDR 2000). In Québec, the combustion of gasoline containing methylcyclopentadienyl manganese tricarbonyl (MMT) as the anti-knock agent also helps to increase the concentration in the air, mainly in high density traffic regions (Zayed 1999a and 1999b).

The annual average of Mn in the air in an urban or rural environment without significant pollution is in the order of 0.01 to 0.07 μg/m^3 (WHO 1981). In regions with large foundries, the total daily respiratory intake may reach 4 to 6 μg, while in regions with ferromanganese and silicomanganese industries, the inhaled dose may reach 10 μg/day (WHO 1981). The Mn content of the air is tending to continually decrease following various control measures. For example, in an American non-urban environment, the quantity was in the order of 60 ng/m^3 (60 nanograms/m^3) from 1953 to 1957, 12 ng/m^3 from 1965 to 1967, and 5 ng/m^3 in 1982 (EPA 1984a). In an urban environment, 110, 73 and 33 ng/m^3 were measured in the same period.

In Canada, Loranger and Zayed (1997a and 1997b) reported 24 ng/m^3 in respirable dust (cyclone with cutoff at 5 μm) and 50 ng/m^3 in total dust (closed 37 mm cassette) in a high traffic zone compared to 15 and 27 ng/m^3 in an area of low traffic density for Montréal where automobiles use a Mn-based anti-knock agent.

---

* 1 milligram (mg) = 1,000 micrograms (μg) = 1,000,000 nanograms (ng)

1.2 Occupational exposure to manganese

Mn and some of its compounds are used in different industrial processes. The most common forms are metallic Mn, Mn^{+2}, Mn^{+3} and Mn^{+4} found mainly as $MnCl_2$, $MnSO_4$, $MnPO_4$, MnO_2 and Mn_3O_4. Alloyed with different metals, mainly iron, Mn makes these products extra hard. Manganese chloride is used as a catalyst but also as an animal food supplement. Manganese dioxide as well as chloride are both used in the manufacture of dry batteries. Manganese dioxide also has several other applications: fireworks, matches and porcelain. Manganese sulfate is used as fertilizer, in ceramics, glazes and varnishes, as a food supplement, as well as a fungicide (ACGIH 2001). Manganese's organic compounds have three main uses: MMT as an anti-knock additive in gasoline, two pesticides, (maneb and mancozeb), as well as mangafodipir used in diagnosing certain forms of hepatic cancers. (ATSDR 2000; ACGIH 2001).

Occupational exposures to inorganic compounds of Mn occur almost solely from the inhalation of dusts and fumes containing Mn. They are mainly related to emissions from automobiles and trucks during maintenance as well as to the dusts from ores during extraction and processing, to steel preparation operations using Mn, in dry battery manufacturing plants, as well as in steel welding operations using manganese and electrodes with high Mn content. (ATSDR 2000; ACGIH 2001; WHO 1986; HSDB 1993)

Concentrations from 1.5 to 450 mg Mn/m^3 have been reported in mines (US EPA 1984a), 0.30 to 20 mg Mn/m^3 in ferroalloy production foundries (Saric et al. 1977), 3 to 18 mg Mn/m^3 in the dry battery manufacturing sector (Emara et al. 1971), from 1 to 4 mg Mn/m^3 in welding operations (Sjögren et al. 1990), and up to 14 mg Mn/m^3 in welding operations with welding wire (CICADS 1999). More recent studies, however, have reported much lower average concentrations of 1 mg/m^3 or less in several of these workplaces (Roels et al. 1985, 1987a, 1987b and 1992; Mergler et al. 1994; Lucchini et al. 1995). For exposed workers, Mn absorption may become much more significant by inhalation than by ingestion through food.

2. METABOLISM AND DISTRIBUTION

2.1 Absorption

Manganese absorption occurs mainly in the gastrointestinal tract after ingestion or in the pulmonary alveoli after inhalation. Gastrointestinal absorption is in the order of only 3 to 5% (Mena et al. 1969; Davidsson et al. 1988; Oberdoerster 1988; EPA 1995b and 1995c). Manganese metabolism in humans is rigorously controlled by homeostatic mechanisms that have an effect mainly on gastrointestinal absorption and excretion. The manganese absorbed through the gastrointestinal pathway is sequestered by the liver. Most of it is excreted by the biliary pathway and is likely to undergo an enterohepatic cycle. Manganese is mainly eliminated in the feces. For workers, the pulmonary inhalation pathway is even more important when the absorption rate is very high and is close to 100% for fine dusts deposited in the alveoli and that are not carried towards the digestive system by the mechanism of mucociliary clearance (ATSDR 2000). Larger dusts deposited at the start of the pulmonary tree are eliminated into the digestive system by the mucociliary process. Morrow (1970) determined a half-life in the order of 66 days in humans after inhalation of submicronic particles.

Another possible source of manganese accumulation and clinical toxicity has been identified in the excessive levels of manganese in parenteral feeding solutions, given intravenously to patients with chronic gastrointestinal diseases (Alves et al. 1997). Also, since manganese is almost completely excreted through the biliary tract, individuals with chronic hepatic insufficiency are at risk of developing hepatic encephalopathy, which would probably be caused by an accumulation of manganese in the brain (Krieger et al. 1995; Pomier-Layrargues et al. 1995).

Several animal studies demonstrate that the determining factor for absorption efficiency is the entry pathway into the body as well as the solubility of the substance containing the Mn in biological fluids (Smith et al. 1995; Roels et al. 1997). Roels et al. (1997) studied the levels of manganese in the blood and brain tissue of rats exposed to repeated doses of Mn chloride and dioxide administered orally, by intraperitoneal injections and intratracheal infusion. Mn chloride (soluble) was rapidly absorbed through these three pathways and distributed to different locations, particularly the brain. However, for Mn dioxide, absorption following an oral dose was very low, while it was absorbed to different degrees in the two other approaches. Higher concentrations of Mn were found after administration of Mn chloride than for the oxide. The authors concluded that the absorption route as well as the nature of the product could be a critical determinant in Mn absorption in the brain. In addition, when Mn dioxide was administered by oral gavage or by intratracheal infusion, the blood levels of Mn increased and then decreased more slowly than when Mn chloride was administered, thus indicating a marked difference in the absorption kinetics of these two substances. The fact that the body reacts more slowly to Mn dioxide suggests that it could remain in the body longer, thus contributing for a longer time to the body burden, even if this occurs at lower concentrations. These data do not allow the impact on human health to be predicted after chronic exposure to low concentrations of manganese dioxide (CICADS 1999).

A study by Tjälve et al. (1996) also demonstrated that the exposure pathway affects Mn absorption. Intranasal infusion of Mn^{+2} in the rat resulted in Mn uptake directly into the olfactory bulb via the olfactory nerve, while intraperitoneal administration only led to a slight increase at

the olfactory bulb. The authors thus suggested that olfactory neurons could serve as an entry pathway for Mn to the brain (Tjälve and Henricksson 1999). These results have been confirmed by several researchers who stipulate that uptake by the olfactory nerve can be substantial (Brenneman et al. 2000; Dorman et al. 2001, 2002; Dorman and Struve 2002; Fechter et al. 2002; Henriksson and Tjälve 2000; Normandin et al. 2002; Vitarella et al. 2000).

There is clear evidence from animal studies that gastrointestinal absorption of Mn is inversely related to the iron concentrations in the diet. Hence, high concentrations of iron lead to a lower absorption of manganese, while low levels of iron promote Mn absorption (Baldwin et al. 1999; Chandra and Tandon 1973; Davis et al. 1992a, 1992b; Diez-Ewald et al. 1968; Rehnberg et al. 1982). Mena et al. (1969) also suggested that low iron absorption would promote Mn absorption.

Finally, note that some animal studies suggest that gastrointestinal absorption of Mn could vary with age (Rehnberg et al. 1980 and 1981). The percent absorption through the gastrointestinal system is in the order of 3 to 5% (Mena et al. 1969; Davidsson et al. 1988; Oberdoerster and Cherian, 1988), while the fine particles deposited deep in the pulmonary tract are probably totally absorbed, and the largest particles in the upper pulmonary tract are carried towards the digestive tract by the mechanism of mucociliary clearance.

2.2 Distribution

Mn is a normal component of any human and animal tissue or fluid. In humans, the concentration in most tissues is in the order of 0.1 to 1 µg Mn/g wet weight (Sumino et al. 1975). Once absorbed, Mn is carried to the organs rich in mitochondria where it is rapidly concentrated. Accumulation in the CNS, following high exposure in animals, occurs slowly and reaches a maximum after approximately 30 days (Stokinger 1981). The normal Mn concentrations in the blood of healthy unexposed workers (4–14 µg/L), urine (less than 10 µg/L) and serum (0.15–2.65 µg/L) are relatively stable and the excess Mn is normally rapidly excreted from the body (ATSDR 2000; Minoia et al. 1990; Davis and Greger 1992; EPA, 1984a; Greger et al. 1990). It therefore becomes difficult to estimate past exposure by measuring Mn in these biological fluids.

Occupational exposure to Mn has shown higher Mn concentrations in the various biological fluids but there is no good correlation with the exposure level (Abel-Hamid et al. 1990; Alessio et al. 1989; Jarvisalo et al. 1992; Roels et al. 1992; Siquiera et al. 1991).

2.3 Metabolism

Mn is an essential element in human nutrition that contributes to the formation of connective tissue and to the metabolism of lipids and carbohydrates (ATSDR 2000; Beliles 1994). Manganese plays a role in bone mineralization, protein metabolism, metabolic regulation, nervous system function (Schroeder et al. 1966; Freeland-Graves et al. 1987; Hurley and Keen 1987; Freeland-Graves and Llanes et al. 1994; Wedler 1994; ATSDR 2000; Beliles 1994), in the protection of cells against free radicals (Doisy 1973) and in the formation of glycosaminoglycans (Wedler 1994) and cholesterol synthesis (Freeland-Graves et al. 1987; Friedman et al. 1987). It also plays an important enzymatic role (Keen and Zidenberg-Cher 1990; NRC 1989; Wedler 1994). It can bind to different substrates such as adenosinetriphosphate or directly to a protein (Keen and Zidenberg-Cher 1990).

2.4 Excretion

Independent of Mn absorption, the homeostatic system generally maintains a stable concentration level by regulating excretion (US EPA 1984a and 1984b). A reserve in the order of 20 mg of Mn is normally stored in the liver and the excess is excreted in the intestine through the bile. Small amounts are also excreted in the urine, skin appendages and perspiration (EPA 1993). The mean urinary concentration is approximately 1 µg/L for an unexposed group. Workers chronically exposed in a foundry had significantly higher urinary excretion than an unexposed control group with a mean concentration of 5.7 µg/L compared to 0.7 µg/L (Alessio et al. 1989). Several other studies confirmed this tendency (Lucchini et al. 1995; Roels et al. 1987a, 1992). For workers who inhaled $MnCl_2$ or Mn_2O_3, approximately 60% of the material initially deposited in the lungs was found in the feces after 4 days (Mena et al. 1969).

2.5 Mechanisms of toxicity *(Also see section 4.3.1.)*

Even if it is known that Mn is a cellular toxin that can damage the nerve impulse transport system, enzymatic activities and receptor functions, the exact way in which Mn neurotoxicity occurs has not yet been clearly established (Aschner and Aschner 1991). Neuropathological changes are detectable in the basal ganglia of people with manganism, and the specific areas affected are located mainly in the striatum and globus pallidus; the substantia nigra is sometimes affected but normally at a lower level (Yamada et al. 1986). Studies on primates have led to the same conclusions (Newland and Weiss 1992). Some authors also report lower levels of dopamine in the caudate nucleus and the putamen in patients (at autopsy) with manganism (Bernheimer et al. 1973).

3. BIOMARKERS

3.1 Exposure biomarkers

Mn can be measured with good sensitivity in biological fluids and tissues, and the levels in the blood, urine, feces and hair have been investigated as potential exposure biomarkers. As a group, workers exposed to 1 mg Mn/m^3 demonstrated statistically higher levels of blood and urinary Mn than an unexposed control group (Roels et al. 1985; Roels et al. 1987b). The results suggested that the blood would be an indicator of body burden, while urine would reflect a recent exposure. Of all the available studies, Lucchini et al. (1995) are the only ones to suggest that blood and urinary Mn levels are correlated with environmental exposures on an individual basis. However, this study has the special characteristic of being the only one that is intended for workers after their exposure has ended and that involves only one substance, MnO_2. In another study intended for chronically exposed and still employed workers, Lucchini et al. (1999) found a positive correlation between the levels of Mn in total dust and the blood level. In this study, no correlation was found between lifetime cumulative exposure and blood Mn. Roels (2002) finally proposes investigating the manganese content of bone tissue using a non-invasive method of analysis by neutron activation, which could be a good representation of the overall body burden. The relationship has not yet been determined and the significance of this approach remains to be documented.

However, several other studies have indicated that, on an individual basis, the correlation between workplace exposure and blood or urinary Mn is not a reliable predictor of exposure (Jarvisalo et al. 1992; Roels et al. 1987b, 1992; Smyth et al. 1973). Furthermore, two studies (Jarvisalo et al. 1992; Roels et al. 1992) suggest that blood and urinary Mn levels can be used to follow the exposure of a group of workers. There is no significant correlation between fecal excretion and occupational exposure (Valentin and Schiele 1983). A study by Baldwin et al. (1999) indicates a correlation between blood Mn levels and high levels of airborne Mn.

Jarvisalo et al. (1992) evaluated the occupational exposure of a few welders to Mn and measured their urinary and blood Mn levels. The level is statistically higher than for unexposed workers and the measurements are only applicable to a group, with the individual result not being very significant.

All of the available data suggest that biological monitoring of blood or urinary Mn levels can be useful in determining whether one group is more exposed than another, but individual values have a very limited significance, except in the case where the individual urinary concentration is much higher than normal, thus indicating an exposure without the possibility of estimating its concentration in the air. Interindividual variability seems very important.

A medical test known as magnetic resonance imaging (MRI) can detect the presence of paramagnetic substances, such as manganese, at abnormal concentrations. This test is used to determine whether a patient has accumulated an abnormally high level of Mn in certain parts of the brain. This tool is sometimes used when a worker shows serious signs of manganese toxicity and must be accompanied by a complete medical history because other substances and other illnesses can also produce an abnormal image (Wolters et al. 1989; ATSDR 2000). Care must be taken because MRI will not necessarily detect Mn after exposure has ended because the body

continually eliminates that substance. MRI demonstrates that Mn is concentrated in the brain at the globus pallidus, striatum and substantia nigra (Mergler 1996; Normandin 2002). An overexposed welder will have a normal MRI 6 months after being removed from the exposure (Mergler 1996). Some people could also retain a high level because their body is inefficient in eliminating Mn. This is the case mainly with people suffering from chronic liver problems (Devenyi et al. 1994; Hauser et al. 1996; Pomier-Layrargues et al. 1998; Spahr et al. 1996; Gasparoti et al. 2002). Gasparoti et al. (2002) report an abnormal MRI of the globus pallidus in 7 examined workers who were exposed to low environmental concentrations of manganese, while Kim et al. (1999) reported an abnormal MRI in 73% of welders exposed to manganese. The MRI as well as a battery of neurobehavioural tests can be useful in determining an overexposure to Mn in the workplace (Dietz et al. 2001; Greger 1998; Lucchini et al. 2000; Nelson et al. 1993). Cheong et al (2002) found a positive correlation between the intensity of the MRI signal and the neurological effects linked to manganese exposure.

These approaches are potentially useful biomarkers but require additional evaluations to determine their validity. Even though it is well established that overexposure leads to higher Mn levels in the body, the correlation between exposure levels, tissue concentrations, and health effects is not well documented. Furthermore, since homeostatic mechanisms prevent fluctuations in Mn in the blood and since Mn is mainly excreted in the bile, identifying a biological marker to estimate the intensity of the exposure or the concentration in the target organ does not seem possible (Lauwerys et al. 1992). In addition, even if the levels in the tissues are increased, they tend to return to normal when the exposure ends (Yamada et al. 1986).

3.2 Biomarkers of effects

Certain biomarkers of effects have been identified but none allows exposure to be related to the quantity measured. These include serum prolactin (Smargiassi and Mutti 1999). Also, the lymphocyte activity of Mn-dependent superoxide dismutase increases with an increase in the amount of Mn absorbed (Yiin et al. 1996). It has been suggested that this enzyme can be useful in determining low and average exposure levels in workers (Davis and Greger 1992; Greger 1999). This enzyme is found in high concentrations in women ingesting manganese supplements, while the levels are depressed in Mn-deficient animals.

For information relating to renal or hepatic effect biomarkers, consult the report of the ATSDR/CDC subcommittee (1990) on biological indicators, and for biomarkers of neurological effects, see OTA (1990).

4. EFFECTS

The main health effects related to manganese exposure are respiratory effects (pulmonary inflammation, pneumonia, reduced respiratory function), extrapyramidal neurologic syndrome of manganism, and preclinical neurological effects as well as reproductive problems (impotence and reduced fertility). Mn does not appear to be a carcinogen, and the effects on other organs will not be described here. The information retained will therefore be limited to these three systems and to the studies carried out on humans: central nervous system, respiratory system and reproductive system and will involve absorption from airborne dusts and fumes, and therefore entering the body first by the respiratory pathway. The reader who wants to know more about absorption pathways, other target organs, or the results on animals may refer to the different review documents including ATSDR 2000, ACGIH 2001, CICADS 1999, RAIS 2002, IRIS 1998, NTP 1993, WHO 1981, 1986, 1987, 1999, 2001 HSDB 2001, Francis and Forsyth 1995, Lundberg 1997, as well as to the original articles in the reference. Mergler and Baldwin (1997) and Iregren (1992 and 1999) have reviewed the neurotoxic effects, while Inoue and Makita (1996) and Pal et al. (1999) have reviewed the clinical aspects.

The relative toxicity of the different Mn compounds is not well known, but inhaled Mn tends to produce more severe toxic effects than ingested Mn. This is probably due to the very different absorption rate related to the entry route: 3 to 5% for the gastrointestinal route (Davidsson et al. 1988, 1989a and 1989b; Mena et al. 1969) and close to 100% for the pulmonary route at the alveoli. This is reflected well in the blood Mn concentration in rats exposed to identical concentrations by inhalation and ingestion (Tjälve et al. 1996; Roels et al. 1997).

4.1 Extrapolation of the results of animal studies to humans

Much information is available in the scientific literature on the toxicological analysis of Mn in animals and humans, but with the large variations in the administered doses, the variety in responses, and the measured differences, inter-species effects cannot easily be extrapolated.

Non-human primates have been a useful model for predicting neurotoxicity in man since the monkey has had neurobehavioral symptoms very similar to humans (Eriksson et al. 1987; Gupta et al. 1980; Newland and Weiss 1992; Shinotoh et al., 1995; Olanow et al. 1996). In addition, the monkey has shown neurological changes resulting from exposure to Mn (Bird et al. 1984). The symptoms noted in the monkey are similar to those observed in overexposed miners and include ataxia, bradykinesia, unsteady gait, grimaces and tremors (Eriksson et al. 1992; Newland and Weiss 1992; Olanow et al. 1996). Also, an accumulation of Mn was noted in the basal ganglia as observed by MRI (Eriksson et al. 1992; Newland and Weiss 1992). This same phenomenon occurs in overexposed workers or in people unable to adequately eliminate Mn (Devenyi et al. 1994; Fell et al. 1996; Hauser et al. 1996; Ono et al. 1995; Pomier-Layrargues et al. 1998; Rose et al. 1999; Spahr et al. 1996). Extrapolation of these results to humans has its limitations because the absorption pathways are different and the inter-species responses can be different.

Available data suggest that neurological effects can occur following chronic exposures in humans and intermediate or chronic exposures in animals. The effects are however seen at lower levels in humans (Bird et al. 1984; Newland and Weiss 1992). These data suggest that animal models,

particularly rodents, can be of limited usefulness for extrapolation to man in establishing dose-response relationships, but can be useful in understanding the mechanisms of these effects.

4.2 Effects on the respiratory system

No study for determining exactly the rate of absorption of inhaled Mn in dusts or fumes was documented in this review. In general, absorption by inhalation is considered as being dependent on particle size since the size will determine the deposition site in the respiratory tree as well as on the solubility of the Mn compound. Very fine particles deposited deep in the respiratory pathway are probably completely absorbed (ATSDR 2000), while particles deposited in the upper tract can be carried into the throat and then the digestive system by the mucociliary clearance mechanism. This latter mechanism has been demonstrated in various studies (Drown et al. 1986; Mena et al. 1969; Newland et al. 1987). Some could also be absorbed at the olfactory nerve (Brenneman et al. 2000; Dorman et al. 2001, 2002; Dorman and Struve 2002; Fechter et al. 2002; Henriksson and Tjälve 2000; Normandin et al. 2002; Tjälve et al. 1996; Vitarella et al. 2000). However, the quantities absorbed at each of the sites are not precisely known.

In humans, the inhalation of Mn particles may lead to an inflammatory response in the lung. This situation is characterized by an infiltration of macrophages and leucocytes that phagocytize the deposited particles (Lloyd Davies 1946). The damage to lung tissue is normally not significant but may include zones of edema (Lloyd Davies 1946). The symptoms and signs of pulmonary irritation may include cough, bronchitis, pneumonitis and minor reductions in pulmonary function (Abdel Hamid et al. 1990; Akbar-Khanzadeh 1993; Lloyd Davies 1946; Roels et al. 1987a). In some cases, chemical pneumonia may be observed among workers exposed to slag and also in Mn mines and in plants producing ferromanganese and potassium permanganate. It is characterized by fever, cough, and often viscous not rusty expectoration, “like thick honey”, and the usual clinical and radiological signs of pneumonia (Lauwerys 1999). The minimum concentration to produce these effects is unknown but industrial experience suggests that several mg/m^3 are necessary to produce these effects. Even if the respiratory effects are similar in different studies (ATSDR 2000), there are no specific biomarkers of effects other than the described symptoms and reduced respiratory function.

As an example, Roels et al (1987a) did a cross-sectional epidemiological study of 141 male workers exposed to inorganic Mn in a plant manufacturing Mn oxides and salts from ore. The average age of the workers was 34.3 years, and seniority varied from 1 to 19 years, with an average of 7.1 years. The results for the workers were compared to a paired control group of 104 workers without Mn exposure. The total mean concentration of Mn in the air varied from 0.07 to 8.61 mg/m^3 during the study, with a respective mean and median of 1.33 and 0.97 mg/m^3. In this study, the authors demonstrated a significantly higher prevalence of cough during cold weather, exertional dyspnea, and episodes of acute bronchitis in exposed workers. These symptoms, measured objectively by respiratory function tests, were slightly different only in exposed workers and smokers. The effects were not related to the Mn concentration in the blood or urine and the authors did not observe any synergistic effects between Mn exposure and tobacco use on any of the spirometric parameters. Other studies suggest, however, a synergistic effect between tobacco use and Mn-related pulmonary effects (Boojar, 2002; Saric et al., 1977).

In the case of welders, inhalation of manganese oxide fumes may lead to chills, fever, sweating, nausea and cough, which is normally called welders’ fever. These symptoms begin 4 to 12 hours

after exposure and decrease after 24 hours. Welders' fever does not normally cause permanent damage unless the exposure is continually repeated (Proctor et al. 1988).

These effects of Mn on the respiratory system were noted mainly with workers exposed to Mn in the workplace but some cases were also noted in populations living near ferromanganese plants (WHO 1987). It was noted in at least one study that the frequency of effects dropped with a reduction in the concentration of total dust in the air. A no observed effect limit value could not be established and the inflammatory response normally begins rapidly after exposure and continues throughout the exposure. This effect is not necessarily specific to Mn and occurs with many inhalable particles (EPA 1985c). This suggests that it is possibly not the manganese itself that causes this effect, but instead the solid particles. An increased prevalence of respiratory illnesses (mainly pneumonia) has been noted in several studies on workers chronically exposed to manganese dust (Lloyd Davies 1946) and for residents who live near ferromanganese plants (WHO 1987; Tanaka 1994). Several authors suggest that this greater susceptibility to lung infections is a consequence of lung irritation and inflammation caused by particulate matter.

4.3 Effects on reproduction

Impotence and loss of libido are common symptoms for workers affected by a clinically identifiable manganism for workers exposed to Mn for periods of 1 to 21 years (Emara et al. 1971; Mena et al. 1967; Rodier 1955; Schuler et al. 1957). Consequently, these symptoms may lead to a lower rate of reproduction.

A statistically lower fertility, established from the average reduction in the number of children per couple, was observed in a cohort of 85 male workers exposed for periods of 1 to 19 years and paired with a control group of 81 people. The total dust concentration varied from 0.07 to 8.61 mg Mn/m^3, with a median value of 0.97 mg Mn/m^3, namely concentrations that did not produce clear cases of manganism (Lauwerys et al. 1985). This suggests that abnormal sexual functions in humans could be one of the earliest clinical manifestations of manganism. No dose-response information was presented such that no NOAEL could be established.

ATSDR (2000) reports that Jiang et al. (1996) conducted an epidemiological reproduction study on 314 men working in Mn plants and with seniority up to 35 years. The geometric mean of Mn in the total airborne dusts was 0.145 mg Mn/m^3 in the form of MnO_2. The researchers found no statistically different difference in reproductive level between the workers and the paired controls, but impotence and a lack of sexual desire were higher in the exposed group. Gennart et al. (1992) carried out a study on 70 paired male workers exposed to a median concentration of 0.71 mg Mn/m^3 in total MnO_2 dust for an average duration of 6.2 years in a dry battery plant. They found no effect on the reproduction rate.

4.4 Effects on the central nervous system

4.4.1. Mechanisms of neurotoxicity

Even though it is known that manganese is a cellular toxin that may damage nerve impulse transport systems, enzymatic activities and receptor functions, the exact way that manganese neurotoxicity occurs has not yet been clearly established (Aschner and Aschner 1991).

A major reduction in dopamine levels in the caudate nucleus, putamen, a reduction in noradrenaline in the hypothalamus and normal serotonin in these regions were observed in a patient with chronic manganese encephalopathy (Bernheimer et al. 1973).

Major histological changes include a marked reduction in myelinated fibers and a proliferation of astrocytes (Yamada et al 1986), thus contrasting with those observed in Parkinson's disease: depigmentation and neural loss in the central nervous system, locus ceruleus and dorsal nucleus of the vagus nerve; occasional presence of Lewy bodies and neurofibrillary tangle in the cerebral cortex.

The harmful effects on the nervous system probably result from the failure of the protective enzymes to detoxify the excess manganese or to change its oxidation potential. In fact, on the one hand, manganese neurotoxicity is based on the capacity of the bivalent form Mn^{+2} to oxidize to the trivalent form Mn^{+3}, the very strong oxidizing form. On the other hand, manganese shows a high affinity for areas rich in neuromelanin, like the nigrostriatal tract (Lydén et al 1984). Thus, manganese promotes the auto-oxidation of dopamine by a transfer reaction of a single electron, generating semiquinones and orthoquinones and the production of toxic free radicals (Donaldson et al 1982; Segura-Aguilar and Lind 1989) which may cause substantial lesions of the dopaminergic system. Cotzias (1976) assumed that, in manganese poisoning, brain dopamine is initially high and then drops.

Wolters et al (1989) examined four subjects with clinical characteristics of mild Parkinson's disease caused by manganese exposure. The MRI and PET scans with 6- fluorodopa were normal, suggesting that in early manganism, damage may occur following post-synaptic functional disturbances in the striatum or even in the neurons of the globus pallidus, rather than a reduction in dopamine as noted in the autopsies of cases of severe manganism.

It cannot be concluded that one simple dysfunction is the basic mechanism of manganese neurotoxicity. It appears more probable that the basic mechanism is multifactorial, involving oxidative stress induced by iron and the direct interaction of manganese with the mitochondria in the terminal part of the dopaminergic nerves, leading to selective mitochondrial dysfunction and resultant excito-toxicity (Verity 1999). This assumption could explain the slow evolution in the disease, the affinity for dopaminergic neurons, and the potential therapeutic advantages of Fe chelation and antioxidants.

4.4.2. Manganism

Chronic Mn exposure may lead to serious damage of the central nervous system (CNS), called manganism. Manganism is a progressive and debilitating syndrome that typically begins with relatively mild nonspecific symptoms that gradually develop. Fully developed manganism may be diagnosed from a characteristic pattern of neurological signs and symptoms (Mena et al. 1967; Rodier 1955; Inoue and Makita 1996), but the early signs and symptoms are not specific to manganese.

A neurological and attentive psychomotor examination paired with known exposure to Mn may allow an increased incidence of preclinical signs of early neurological effects to be detected in apparently healthy people (Iregren 1990; Roels et al. 1987a). However, these tests are not sufficiently specific to determine whether an individual has been exposed to too high levels of Mn

and also, no biochemical indicator is currently available for detecting early neurotoxic effects that could clearly indicate prolonged Mn overexposure. Magnetic resonance imaging tests (MRI) (Lucchini et al 2000) and positron-emission tomography (PET) help in diagnosing manganism and in differentiating it from Parkinson's disease (Pal et al. 1999). Contrary to Parkinson's disease, the effectiveness of treatment with levodopa is controversial (Lu et al. 1994).

In a recent review, Pal et al (1999) described the clinical syndrome of Mn neurotoxicity as being roughly divided into three stages based on the predominant manifestations: i) behavioral changes, ii) the specific features of manganism, and iii) dystonia accompanied by severe gait problems.

Early symptoms of neurological damage that can be attributed to manganese may include subjective symptoms, sometimes associated with fatigue, headache, muscle cramps, lumbago, a loss of appetite, apathy, insomnia or drowsiness, a loss of memory, reduced concentration, reduced libido, impotence and reduction in speed of movement (Pal et al. 1999). Other authors also report sadness, a changed gait, fine tremors, lassitude (an individual's progressive loss of strength), weakness in the legs, anorexia, nervousness and irritability (Fairhall 1957; Rodier 1955; Whitlock et al. 1966; Mena et al. 1967; Tanaka & Lieben 1969; Sjögren et al. 1996; Pal et al. 1999). These signs are frequently accompanied by aggressive or destructive behaviors and strange compulsive activities such as laughing or spasmodic uncontrollable outbursts or impulses to sing or dance. Patients are aware of their situation but are unable to control their behavior (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; Pal et al. 1999).

Subsequently, extrapyramidal signs appear. Speech becomes slow or hesitating, without tone or inflection, a dull facial expression without emotion often interrupted by a spasmodic laugh or a dystonic grimace, slow and awkward limb movement, difficulty writing (Rodier 1955; Schuler et al. 1957; Mena et al. 1967; Tanaka and Lieben 1969; Smyth et al. 1973; Yamada et al. 1986; Ky et al. 1992; Wennberg et al. 1991; Hochberg et al. 1996; Mergler and Baldwin, 1997, Pal et al. 1999). The atypical signs of Parkinson's disease may also include difficulty getting out of a low chair, anteropulsion, retropulsion and torsion en bloc. Patients show particular difficulty in walking backwards because they become unstable and tend to fall (Huang et al. 1989; Pal et al. 1999).

In the most advanced cases, patients develop a syndrome similar to Parkinson's disease that is often accompanied by severe dystonia of the trunk and extremities. Walking becomes difficult and a characteristic erratic gait develops, "cock-walk", with the patient walking on his toes with his arms bent and body leaning forward (Huang et al. 1993, 1998; Pal et al. 1999; Calne et al. 1994).

The muscles become hypertonic and voluntary movements may be accompanied by slight tremors (Chu et al. 1995; Mergler and Baldwin 1997). In some cases, psychological disturbances called manganese psychosis and manganese mania precede or accompany the final stages of the disease (Rodier 1955; Mena et al. 1967; Cook et al. 1974; Mergler and Baldwin 1997).

Some clinical symptoms as well as magnetic resonance imaging (MRI) and positron-emission tomography (PET) tests can help differentiate manganism from Parkinson's disease. Barbeau (1984) noted that hypokinesia and tremors in patients with manganism differ from those in Parkinson's. Calne et al. (1994) also noted other differences with Parkinson's disease: psychiatric

disturbances early in the disease, "cock-walk", a propensity to fall when moved, less frequent tremors at rest, more frequent dystonia and the lack of response to certain medications used in Parkinson's disease. Other pathological differences have also been described (Barbeau 1984; Beuter et al. 1994; Calne et al. 1994; Pal et al. 1999).

The majority of cases of manganism reported in the literature came from operations in mines where concentrations were extremely high and could reach 900 mg/m^3 (Flinn et al. 1990; Rodier 1955) or in foundries (Whitlock et al 1966; Smyth et al. 1973). Schuler et al. (1957) documented chronic Mn poisonings in miners exposed chronically and in which one third of the air samples exceeded 5 mg/m^3. The latency period varies from a few months to a few decades. Some symptoms of manganism can improve following treatment, but this situation is normally of short duration and brain damage is not only permanent but tends to progress, even after the exposure ends (ATSDR 2000). The main symptoms encountered in the workplace outside mines are less severe than manganism and are mainly related to difficulty keeping hands steady, doing rapid hand movements, and keeping one's balance, thus suggesting that the effects are related to the exposure concentration (ATSDR 2000). Several case studies are reported in the literature.

Tanaka and Lieben (1969) reported 7 cases of manganism and 15 cases at the diagnosis limit in 144 workers exposed to manganese dusts or fumes at concentrations above 5 mg/m^3. No case was reported in 48 workers exposed to less than 5 mg/m^3.

4.4.3. Differences and similarities between manganism and Parkinson's disease

The characteristics of clinical manganese neurotoxicity resemble those of idiopathic Parkinson's disease. Nonetheless, a careful analysis of manganese poisoning cases by Calne et al. (1994) and Feldman (1999) revealed clinical, pathological, pharmacological and imaging differences.

Similarities in the clinical landscape include the presence of generalized bradykinesia and extensive rigidity, while the dissimilarities are represented in manganism by: a) less frequent tremors at rest; b) more frequent dystonia; c) a particular tendency to fall backwards; d) failure in obtaining a sustained therapeutic response with antiparkinson drugs; and e) failure to detect a capture reduction of fluorodopa in the PET-scan.

On the anatomo-pathological aspect side, the few autopsies carried out on cases of Mn-induced Parkinson's disease mainly demonstrated degenerative lesions of the globus pallidus and "sub-thalamic nucleus, caudate nucleus and the putamen, with less frequent and less severe injury to the substantia nigra. This is a manifestation typically different from that of idiopathic Parkinson's disease in which the substantia nigra is typically involved and the pallidostriatal complex is not involved (Yamada et al. 1986). The globus pallidus is known as being sensitive to energy deprivation and to abnormal excito-toxicity injury and it contains neurons and dopaminergic receptors. However, even though manganism and Parkinson's disease seem to be two different entities, several observations have been made in the past on the possible role of manganese exposure in the etiology of Parkinson's disease.

In fact, even though Parkinson's disease is one of the most common neurological diseases, its etiology is still unknown and the hypothesis of an interaction between environmental factors and an individual genetic susceptibility has been raised (Calne 1983; Bleecker 1998; Zuber and Alperovitch 1991). In particular, a possible relationship between Parkinson's disease, agricultural

work and the use of pesticides has been suggested (Barbeau et al 1987; Hertzman et al 1990; Goldsmith et al 1990; Semchuck et al 1992; Engel et al. 2001; Di Monte et al. 2002).

4.4.4. Treatment

Starting with the hypothesis that the main mechanisms of neurotoxicity are free radicals and the oxidative stress that they generate, some studies have examined the possible benefits of antioxidant agents in neurobehavioral deficits with very variable degrees of success.

It is already known that antiparkinson drugs may have a positive effect on manganism's symptoms and signs, but these positive effects are only temporary and usually of short duration. Some authors have attributed these temporary benefits to the placebo effect (Lu et al 1994).

Chelation therapy, mainly using $CaNa_2EDTA$, has been used with variable success in acute and chronic cases of poisoning (Discalzi et al. 2000; Hernandez et al 2002; Komaki et al 1999; Fitzgerald et al 1999).

The main treatment therefore consists of stopping exposure in the early phase of the illness when the signs and symptoms appear to be still reversible. This requires detection of the early signs.

4.4.5. Early neurological effects

It has been suggested that the health effects, particularly on the central nervous system, occur in a "continuum of dysfunction" which would be dose-related (Mergler et al. 1999; ATSDR 2000; ACGIH 2001). In other words, slight and imperceptible effects may be caused by low but physiologically excessive quantities of Mn and these effects increase in severity when the exposure level and the exposure duration increase. Mergler et al. (1999) have described the progression towards manganism as a slow deterioration in well-being, which can initially be detected as early neurofunctional changes detectable solely in exposed groups; later, as individual preclinical and then clinical signs; and finally, as a complete neurological disease, manganism, whose development depends on the exposure dose, the exposure duration and individual susceptibility.

The epidemiological and case studies reported in this section address this continuum of dysfunction and help reveal the apparent dose-response relationship. It is clear that chronic exposure to very high concentrations of manganese may lead to permanent neurological damage, as seen in the cases of highly exposed miners who develop manganism. Chronic exposures to much lower concentrations such as those currently found in the workplace have been associated with different neurological deficits including the capacity to perform rapid hand movements, some loss of coordination and balance, and an increase in symptoms such as forgetfulness, anxiety or insomnia. However, the minimum level is still not known where no effect occurs on the central nervous system (NOAEL) following chronic exposure to a low concentration. Only the epidemiological studies most frequently cited in the literature will be reported in this document. These early neurotoxic effects have been reported at exposure concentrations in the air of 0.027 mg Mn/m^3 to 1 mg Mn/m^3.

A group of 60 welders from 3 different plants (20 per plant) were studied by Chandra et al (1981) and paired with 20 unexposed workers. The electrodes used in plants A, B and C contained 2.10%, 0.55% and 0.45% manganese respectively, while the mean concentrations of Mn in the breathing zone were 0.31 (0.044 to 0.99), 0.57 (0.50 to 0.80) and 1.74 mg Mn/m^3 (0.88 to 2.6) respectively. Several welders complained of lung problems and insomnia. The average age was 42.6, 43.1 and 35.7 years respectively. The average seniority in plant A was more than 10 years. In plant B, 3 welders had less than 2 years of seniority, and the others had more than 20. In plant C, half of the welders had been there for less than 10 years and the other half for more than 15 years. Neurological tests demonstrated abnormal functions in 5 workers in plant A, 10 in plant B, and 9 in plant C, respectively. The authors reported only recent exposures without being able to document past exposures. Nevertheless, 40% of the welders showed abnormal neurological functions at a maximum documented concentration of 2.6 mg Mn/m^3.

Among the studies most frequently cited in the literature, Roels et al (1987a and 1987b) did a cross-sectional epidemiological study of a cohort of 141 clinically healthy male workers exposed to inorganic Mn in a plant producing Mn oxides and salts from ore. The average age of the workers was 34.3 years (range from 19 to 59 years), and seniority varied from 1 to 19 years with an average of 7.1 years. The results for the workers were compared to a paired control group of 104 workers without exposure to Mn. The total average concentration of Mn in the air varied from 0.07 to 8.61 mg/m^3 during the study, with a respective average and median of 1.33 and 0.97 mg/m^3. The authors used questionnaires and carried out standardized neurological examinations as well as psychomotor tests (hand tremors, short-term memory, and simple reaction time). The prevalence of subjective symptoms did not vary significantly between the controls and the exposed workers, except for fatigue, finger tremors and irritability. The standardized neurological examination demonstrated no difference between the exposed workers and the control groups except for body rigidity. However, the psychomotor tests revealed that the workers exposed to Mn had a significantly longer reaction time, performed significantly less well in the audio-verbal short-term memory test, and had a significant difference in the prevalence of abnormal values in hand-eye coordination tests and hand steadiness parameters. This study suggests that a time-weighted average exposure value (TWA) of 1 mg/m^3 of Mn for total dust may result in the appearance of preclinical pulmonary and CNS effects in workers exposed for less than 20 years.

Iregren (1990) carried out a study on 30 workers in Swedish foundries paired with a control group of 60 unexposed people. The inhalation exposure concentrations varied from 0.02 to 1.4 mg/m^3 of total dust with a median of 0.15 mg/m^3 of total dust, and the exposure time varied from 1 to 35 years with an average of 9.9 years. Neurobehavioral and manual dexterity functions were evaluated and significant differences in relation to the control group were reported for the simple reaction time and manual dexterity. The performances were also not as good for exposed workers in the rapid alternating hand movement tests. Effects had been noted at exposures below 0.2 mg Mn/m^3 of total dust.

More recently, Roels et al. (1992) carried out another cross-sectional epidemiological study on 92 male workers exposed to MnO_2 in a dry battery manufacturing plant. The average age of the workers was 31.3 years (22.0 to 49.6) with an average seniority of 5.3 years over a range from 0.2 to 17.7 years. The results were compared to a paired control group of 101 unexposed workers. The geometric mean of the exposure concentrations was 0.215 mg Mn/m^3 (0.021 to 1.317 mg Mn/m^3) for the respirable fraction and 0.948 mg Mn/m^3 (0.046 to 10.840 mg Mn/m^3) for total dusts. In this study, the total dust concentrations were strongly correlated with the respirable

fraction corresponding on average to 25% of the Mn content of the total dust. The lifetime integrated exposure value for Mn exposure in the respirable fraction was evaluated for each worker and is therefore expressed as mg Mn/m^3-year. The geometric mean of the respirable dust concentrations was 0.793 mg Mn/m^3-year with a range from 0.040 to 4.433 mg Mn/m^3-year, while the geometric mean for total dust was 3.505 mg Mn/m^3-year with a range from 0.191 to 27.465 mg Mn/m^3-year.

On a group basis, the blood (0.81 *vs* 0.68 µg/100mL) and urinary (0.84 *vs* 0.09 µg/g creatinine) Mn concentrations measured in the study of Roels et al. (1992) were higher than those in the control group. However, on an individual basis, no significant correlation was found between these biological parameters and different external parameters such as the exposure duration or the integrated exposure. On a group basis, they found a significant relationship between the level of urinary Mn and the level of Mn in the air. The analysis of questionnaires on perceptions of neurotoxic problems showed no significant difference between the exposed workers and the control group. However, the exposed workers performed less well on several tests. In fact, the exposed workers showed a significantly longer visual reaction time than the control group. The results for five eye-hand coordination parameters were more erratic in the exposed workers than in the control group. Also, the results measuring hand steadiness demonstrated a systematic tendency towards higher hand tremor results. Even though the workers exposed to Mn performed less well in the audio-verbal short-term memory tests than the control group, the average scores relating to memory and word recognition were not significantly different. From the analysis of these results, the authors concluded that hand tremors represent the most appropriate parameter for defining an exposure limit. They concluded from their study that lifetime integrated exposure to total dusts of Mn greater than 3575 µg Mn/m^3-year or respirable dusts greater than 730 µg Mn/m^3-year may lead to an increased risk of tremor. This quantity corresponds to an average exposure to Mn in respirable dust of 37 µg Mn/m^3 for a period of 20 years. From these results, Roels and Lauwerys (1992) suggested a TWA of 90 µg Mn/m^3 of total dust or 18 µg Mn/m^3 of respirable dust for standards of 8 hours per day and targeting a career of 40 years. These levels aim to protect the majority of workers from developing early neurotoxic effects related to occupational exposure to Mn.

Chia et al (1993a et 1993b) studied two small groups of workers (N=17, N=13) from two paired manganese plants (N=17 and N=18) to maintenance workers in a hospital and manual workers without exposure to neurotoxic agents. The average exposure was 7.4 years and, before 1985, the exposures exceeded 5 mg Mn/m^3. For the 1981 to 1991 period, the average exposure was 1.59 mg Mn/m^3. In a first article, they reported that the exposed workers did not perform as well as the controls in motor function, memory and other intellectual function tests. In a second article, the researchers reported that the postural stability of exposed workers was not as good as for the control group. These studies provided little information on the effect of exposure concentrations since the exposures were drastically reduced during the period of the study and the reported blood and urinary Mn concentrations were much higher than in the other studies found in the literature.

Mergler et al. (1994) did a cross-sectional epidemiological study in a ferromanganese and silicomanganese alloy plant on a cohort of 115 paired workers. The workers were exposed to manganese fumes and dusts. The total dust level varied from 0.014 to 11.48 mg/m^3 (median of 0.151 mg/m^3 and arithmetic mean of 1.186 mg/m^3) while the respirable dusts ranged from 0.001 to 1.273 mg/m^3 (median 0.032 mg/m^3 and arithmetic mean of 0.122 mg/m^3). All the dust levels reported had been evaluated as stationary samples. The average age was 43.4 ± 5.4 years with an

average exposure duration of 16.7 years ± 3.2 years. The exposed workers showed statistically higher levels of blood Mn (1.03 *vs* 0.68 µg/100mL) but no significant difference in urinary manganese was measured. The authors reported differences in the symptoms reported, in the emotional state, particularly tension, anger, fatigue and confusion. Some motor functions were modified in relation to the controls, particularly in rapid alternating hand movements. Cognitive flexibility and the olfactory perception threshold were also different in the groups of exposed workers. Damage to the central nervous system occurs according to a continuum of effects.

Lucchini et al. (1995) carried out a study on a cohort of 58 asymptomatic workers in a ferroalloy plant. Seniority varied from 1 to 28 years (average 13 ± 7) and the exposure to total MnO_2 dust varied from 0.070 mg/m^3 to 1.59 mg/m^3. Over the last 10 years, exposure had been reduced to a range from 0.027 mg/m^3 to 0.270 mg Mn/m^3 in total dust. The workers were examined during a forced temporary layoff over a period of 1 to 42 days following the last exposure. The authors found a correlation between blood Mn levels and performances in addition, finger tapping, and number and symbol memory tests. However, no correlation was found for the reaction time test. It is the only study in which a correlation was found between urinary and blood concentration and lifetime cumulative exposure. According to the authors, this situation may possibly be due to the fact that it is the first study involving workers no longer exposed to Mn in the recent past (1 to 42 days), particularly when the correlation coefficients increased in relation to the time without exposure.

Sjögren et al. (1996) studied the effects on the nervous systems of welders exposed to manganese or aluminum. For manganese, 12 welders whose average age was 40.4 years (range from 27 to 61 years) were evaluated. Each had worked for more than 100 hours with electrodes with a high manganese content (22 to 24% Mn in the fumes) and less than 25 hours with lead and aluminum, two other neurotoxic substances. The average exposure to manganese was 270 hours (100 to 1760 hours) and the welders showed reduced motor function in several tests despite the fact that their blood manganese level was no higher than in the controls. The results for these welders were not as good as for the controls for sleep disturbances, finger tapping speed, hand dexterity, and memory. These results corroborate those obtained by these researchers in their 1990 study.

In another study, Lucchini et al. (1999) looked at the neurotoxic effects associated with long-term exposure to increasingly lower concentrations of Mn oxides (MnO_2 and Mn_3O_4) in a ferroalloy plant with a cohort of 61 workers paired with 87 unexposed controls. The mean concentrations of dust changed in the company from 1981 to 1997. In the furnace zone, the geometric mean of the total dust concentrations dropped from 1597 µg Mn/m^3 in 1981 to 239 µg Mn/m^3 in 1997. In the casting area, the concentration increased from 151 to 255 µg Mn/m^3. In the welding operations, it dropped from 167 to 54.7 µg Mn/m^3 during the same period.

The researchers divided the group into three: high exposures with mean concentrations of Mn in the total dusts that dropped from 1.6 to 0.165 mg Mn/m^3, average concentrations (0.151 to 0.067), and low concentrations (0.057 to 0.012). The Mn content in the total dust corresponded to approximately three times the geometric mean and 2.6 times the arithmetic mean of that in the respirable dust. The blood and urinary manganese levels were significantly higher in the exposed individuals than in the controls. The researchers noted much fewer complaints from the workers than in the study of Mergler et al. (1994).

The performances of these workers, who had been tested in 1990 and 1991, did not improve over time or with the reduction in the exposure level. An average cumulative exposure index (CEI) was determined for each worker and the cumulative geometric mean index was 1205 μg Mn/m^3-year. Significant differences in several neurotoxic tests were noted between the groups with a low CEI (<0.5 mg Mn/m^3-year), average CEI (0.5 to 1.8 mg Mn/m^3-year) and high CEI (>1.8 mg Mn/m^3-year).

A higher prevalence of symptoms was established for exposed workers than for the control group for irritability, loss of balance and rigidity. The tremor parameters, including the central frequency and its dispersion, were statistically different in the exposed workers. The motor functions of rapid alternating movement coordination and memory functions were reduced. A dose-effect relationship was observed between the cumulative exposure index and some of the test results. The authors concluded that for the worker to be protected by the exposure throughout his professional life, the mean concentration should be less than 100 μg Mn/m^3 in total dust and 38 μg Mn/m^3 in respirable dust.

Gibbs et al. (1999) studied a cohort of 75 workers exposed to Mn in an American electrolytic metal production plant, paired with controls. Personal exposure levels were established for each of the 12 types of jobs (Mn in total and respirable dusts) and the mean exposure was 0.066 ±0.059 mg Mn/m^3 in respirable Mn (median of 0.051 mg Mn/m^3) and 0.18 ± 0.21 mg Mn/m^3 (median of 0.086 mg Mn/m^3) in total dusts. The answers to a questionnaire were similar for the exposed individuals and the control group. The study of Gibbs et al. (1999) is the first that does not report any effects on the central nervous system of workers exposed chronically to manganese.

Iregren (1992) reviewed psychological tests for neurotoxic effects and reported a consistent image of the effects on the rapidity of response, motor functions and memory. The consistency of that image is somewhat weakened by the results of Lucchini (1992) and Mergler (1992) which do not always demonstrate a consistent sensitivity for the rapidity of response, motor function and memory tests. In a second review involving 13 studies, Iregren (1999) concluded that each study, taken individually, has deficiencies, but that overall, 12 of the 13 studies indicate effects attributed to Mn exposure. He concludes that these effects are encountered even at concentrations below 0.2 mg Mn/m^3 in total dusts. The author reminds us that the tests used in these early screenings are significant in group studies but cannot be used to evaluate an individual worker. Mergler and Baldwin also published such a review in 1997.

4.4.6. Reversibility of neurotoxic effects

Few data are available on the reversibility of the neurotoxic effects associated with chronic Mn overexposure. The researchers believe that the effects are rather irreversible (Ellenhorn and Barceloux 1988). However, there is some evidence that recovery may occur when the exposure stops (Smyth et al. 1973). Antiparkinson drugs such as levodopa have been able to reverse some of the neuromuscular signs of manganism (Ejima et al. 1992; Rosenstock et al. 1971), but these drugs have several side effects and reports indicate that they do not improve the patients' neurotoxic symptoms (Calne et al. 1994; Chu et al. 1995; Cook et al. 1974; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Huang et al. 1989). The ATSDR review (2000) reports that symptoms of manganism can be improved by certain medical treatments, but the improvement is generally temporary and damage to the brain permanent.

Huang et al (1993, 1998) documented the progression of manganism in five workers chronically exposed to Mn in the ferroalloy sector. These workers were examined up to 10 years after the cessation of all exposure and the average score for Parkinson's disease went from 15.0 ± 4.2 in 1987 to 28.3 ± 6.7 in 1991 and then to 38.1 ±12.9 in 1995 for their patients then between 48 and 56 years of age and after 3 to 13 years of lifetime exposure. The examination showed a continual deterioration in health status in gait disturbance, foot tapping speed, rigidity and in writing. Bradykinesia, getting up from a chair, and stability had also deteriorated. Muscle pain, cramps, oral expression, fatigue, and difficulty sleeping and writing also tended to deteriorate. Even though high Mn levels were found in biological fluids at the initial diagnosis, withdrawal from exposure for a prolonged period led to a return to low levels of Mn in biological fluids. Analysis using magnetic resonance imaging showed no region with an abnormally high Mn concentration. These results show that the disease continues to progress even 10 years after leaving the workplace.

Roels et al (1999) carried out an eight-year longitudinal study on the same cohort as that studied in 1992 in order to determine the reversibility of three neurotoxic effects: hand-eye coordination (HEC), hand steadiness (HS), and simple visual reaction time (SVRT). The control group consisted of 37 workers in a neighboring company where manganese exposure was zero. The workers were followed as the ambient concentrations were better controlled, and therefore the workers were increasingly less exposed. In addition, during this period, some of the workers left the company and were integrated into the study so that the effect of total absence of exposure could be measured. The cohort became smaller during the study but no departure was related to neurological symptoms or signs. The overall reduction in exposure went from approximately 800 μg Mn/m^3 in 1987 to approximately 250 μg Mn/m^3 in 1995. The workers were divided into three groups based on their exposure level: the group (n=23) with low exposure to total dusts (0.16 to 0.31 mg Mn/m^3), the median exposure group (n=55) from 0.25 to 0.90 mg Mn/m^3, and the high exposure group (n=14) from 1.2 to 3.0 mg Mn/m^3 in total dust. The average age was 38.5 years (range from 32 to 51 years) and exposure data were available for personal sampling for total and respirable dusts.

From this study, Roels et al. (1999) concluded that the tests used were reproducible and reliable throughout the study. They also demonstrated that past severity of the Mn exposure determined the relative significance of the loss in precision in hand and forearm movement (HEC) in exposed workers as compared to the control group as well as their recovery potential. The authors noted a deterioration in the precision of hand-arm movements between 1987 and 1990 and then a subsequent improvement. In fact, in the two most exposed subgroups, recovery was only partial following a high reduction in exposure, while it was total in the less exposed group, demonstrating a partially reversible effect for this parameter. However, for the two other tests, HS and SVRT, no recovery was noted, suggesting that these conditions are irreversible. The study on ex-employees of this company confirmed the results obtained, namely that one of the three effects is partially reversible, while the two others are irreversible.

5. CURRENT STANDARDS AND RECOMMENDATIONS

5.1 Current standards

Several countries have established standards for exposure to manganese in the air. These standards have force of law and companies must comply with these levels in laws relating to the quality of the work environment. Each of the countries has its own process for determining the level of its standards. A few of these standards are listed in Table 1 and include the quality of workplace air and of the general outdoor atmosphere.

Table 1: Standards of a few countries relating to manganese and its compounds

Substance	Organization/ country	TWA/STEL mg Mn/m^3	Explanations	References
Fumes	CSST/Québec HSE/Great Britain	1.0 / 3.0		RSST 2001 ATSDR 2000
Fumes	OSHA/ U.S.	5.0	Ceiling value	OSHA 1998 (29 CFR 1910.1000) (Table Z-1)
Total dusts	CSST/Québec HSE/Great Britain	5.0		RSST 2001 ATSDR 2000
Mn cyclopenta-dienyl tricarbonyl	CSST/Québec OSHA / U.S.	0.1	Percutaneous absorption	RSST 2001 OSHA 1998 (29 CFR 1910.1000) (Table Z-1)
Manganese methyl cyclo-pentadienyl tricarbonyl	CSST/Québec	0.2	Percutaneous absorption	RSST 2001
Manganese tetroxide	CSST/Québec HSE/Great Britain OSHA/ U.S.	1.0		RSST 2001 ATSDR 2000 OSHA 1998 (29 CFR 1910.1000) (Table Z-1)
Manganese	NAOHS/Australia	1.0	Dusts and fumes	ATSDR 2000
Manganese methyl cyclo-pentadienyl tricarbonyl	EPA	BANNED		EPA 1978, 1979, 1981, 1995a
Elementary Mn and inorganic compounds	OSHA/ U.S.	5.0	Ceiling value	OSHA 1998 (29 CFR 1910.1000) (Table Z-1)
Elementary Mn and inorganic compounds	Germany	0.5	MAK value	DFG 2000

5.2 Current guidelines

Some organizations such as the ACGIH, EPA and WHO do literature reviews in order to integrate the most recent scientific knowledge into the evaluation procedure for human health risks and for levels that would be safe for maintaining the health of the majority of workers throughout their professional careers or of the general population including children and senior citizens for their entire lives. Such organizations have proposed guidelines without force of law that are not standards but that aim, based on current scientific knowledge, to establish levels that should not be exceeded so as not to compromise the health of workers or the general population. The current trend in these organizations or groups of researchers is to prevent early injury to the central nervous system and to other target organs.

Table 2 below presents some of these values relating to occupational exposure to manganese as well as the exposure of the general population to environmental pollution.

Table 2: A few guidelines for manganese exposure

Organization	Environment	Description	Guideline mg/m^3	Reference
WHO	Workplace	Respirable dusts	0.30	WHO 1986
WHO	Outdoor air	Quality of the outdoor air (annual average)	0.00015	WHO 1997
ACGIH	Workplace	Total dusts Respirable dusts (under consideration)	0.2 0.03 (under consideration)	ACGIH 2001 ACGIH 2002 (notice of intended changes)
EPA	Outdoor air	Quality of the outdoor air	0.00005	IRIS 1998
NIOSH	Workplace	Dusts and fumes	1.0	NIOSH 1997
NIOSH	Workplace	Dusts and fumes-STEL	3.0	NIOSH 1997

The reasoning used by these organizations to come to these proposed values is described briefly here based on the ACGIH example.

The ACGIH (2002) is currently considering the possibility of reducing its proposed TLV to go from 0.20 mg Mn/m^3 in total dust to 0.03 mg Mn/m^3 in respirable dust for a worker working 40 hours per week. This proposed change, currently under study, is based first on the prevention of early neurotoxic effects but also on the prevention of respiratory and reproductive effects. At the present time, a dose-response relationship could not be established from all the epidemiological studies available, but early signs of central nervous system injury by inhalation have been observed at levels from 0.027 to 1.0 mg Mn/m^3 (Chia et al. 1993a, 1993b, 1995; Iregren 1990; Lucchini et al. 1995; Mergler et al. 1994; Roels et al. 1987a, 1992; Wennberg et al. 1991) while cases of manganism have been reported at levels as low as 2 to 22 mg/m^3 (Cook et al. 1974; Rodier 1955; Saric et al. 1977; Schuler et al. 1957; Tanaka and Lieben 1969; Whitlock et al. 1966). These neurotoxic effects were observed following exposures varying from 1 to 35 years

(Schuler et al. 1957; Whitlock et al. 1966; Tanaka and Lieben 1969; Cook et al. 1974; Saric et al. 1977; Roels et al. 1987a, 1992; Iregren 1990; Wennberg et al. 1991; Chia et al. 1993a, 1993b, 1995; Mergler et al. 1994; Lucchini et al. 1995). In the case of manganese, Roels' studies, which were corroborated by several other studies, are the most used ones, and the majority of the organizations use these results as a basis for proposing target values based on their respective approaches.

6. CONCLUSION

Manganese is an essential trace element, but occupational overexposure to manganese may lead to disturbance in homeostatic control and produce different health problems: injury to the central nervous system, lung problems and reproductive effects.

The most serious damage is to the central nervous system and an overexposed worker may develop an occupational disease called manganism. Many cases have been reported in the literature and the majority of them were at very high exposures in the mining industry. Cases were also reported in foundries and with welders at lower concentrations of 2 mg Mn/m^3 or more. This disease develops progressively, and studies over the last 15 years have revealed a series of early effects on the central nervous system at concentrations below 1 mg Mn/m^3 in total dusts. From the studies of Roels and Iregren, the ATSDR (2000) determined a NOAEL of 0.07 mg Mn/m^3 in respirable dust. This value is confirmed by the study of Gibbs (1999) in which no effect was observed at a median concentration of 0.051 mg Mn/m^3.

Current Québec standards are similar to the American, British and Australian standards but the organizations and groups of researchers in this field currently favor making these standards more restrictive in order to take into account early effects on the central nervous system.

Although work-related neurotoxic risks today rarely reach the level of the pathologies of previous decades, exposure to manganese can still cause changes in certain higher brain functions of the CNS. The corollary is that a series of tests should be assembled that are capable of evaluating the cerebral integration functions that are affected the earliest during chronic exposure to manganese. These batteries of tests could be used for detecting early signs and symptoms of poisoning and also for the medical monitoring of workers with early signs and symptoms and who could be removed from work or moved to work areas where the exposure is lower and acceptable.

A complete program to strictly control occupational exposures remains the best means of prevention for avoiding health effects caused by manganese in the workplace.

7. BIBLIOGRAPHY

Documents preceded by an asterisk are summary review documents

Abdel-Hamid MM, El-Desoky SA and Magdi SM, 1990. Estimation of manganese in blood between exposed workers to different concentrations at industrial units. Egypt J Pharm Sci 31:143-150.

*ACGIH, 2001. Manganese and Inorganic Compounds, Documentation of TLV's. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

ACGIH, 2002. TLVs and BEIs. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

Akbar-Khanzadeh F, 1993. Short-term respiratory function changes in relation to workshift welding fume exposures. Int Arch Occup Environ Health 64:393-397.

Alessio L, Apostoli P, Ferioli A et al., 1989. Interference of manganese on neuroendocrinal system in exposed workers. Preliminary report. Biol Trace Elem Res 21:249-253.

Alves G, Thebot J, Tracqui A, Delangre T, Guedon C and Lerebours C, 1997. Neurologic disorders due to brain manganese deposition in a jaundiced patient receiving long term parenteral nutrition. J Parent Enter Nutr 21:41-45.

Aschner M and Aschner JL, 1991. Manganese neurotoxicity: cellular effects and blood-brain barrier transport. Neurosci Biobehav Rev 15:333-340.

ATSDR/CDC, 1990. Subcommittee report on biological indicators of organ damage. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta GA.

*ATSDR, 2000. Toxicological Profile For Manganese (updated). Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services. PB2000108025, September.

Baldwin M, Mergler D, Larribe F, Bélanger S, Tardif R, Bilodeau L, Hudnell K, 1999. Bioindicator and exposure data for a population based study of manganese. Neurotoxicology 20:343-354.

Barbeau A, 1984. Manganese and extrapyramidal disorders (a critical review and tribute to Dr. George C. Cotzias). Neurotoxicology 5:13-35.

Barbeau A, Roy M, Bernier G, Campanella G and Paris S, 1987. Ecogenetic and Parkinson's disease prevalence and environmental aspects in rural areas. Can J Neurol Sci 14:35-42 .

Beliles RP, 1994. The Metals. In: Patty's Industrial Hygiene and Toxicology, 4th ed., Vol.II, Part C, Toxicology, pp. 2106-2124. GD Clayton and FE Clayton, Eds. John Wiley & Sons, New York.

Bernheimer H, Birkmayer W, Hornykiewicz O et al., 1973. Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. J Neurol Sci 20:415- 455.

Beuter A, Mergler D, de Geoffroy A, Bélanger S, Carrière L, Varghese L, Skeekumar J and Gauthier S, 1994. Diadochokinesimetry: a study of patients with Parkinson's disease and manganese-exposed workers. Neurotoxicology 15:655-664.

Bird ED, Anton AH and Bullock B, 1984. The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey. Neurotoxicology 5:59-65.

Bleecker ML, 1998. Parkinsonism, a clinical marker of exposure to neurotoxins. Neurotoxicol and Teratol 10:475-478.

Boojar MM et al, 2002. "A longitudinal follow-up of pulmonary function and respiratory symptoms in workers exposed to manganese". J. Occup Environ Med, 44:282-290.

Brenneman KA, Wong BA, Buccellato MA, Costa ER, Gross EA, Dorman DG, 2000. Direct olfactory transport of inhaled manganese ($^{54}MnCl_2$) to the rat brain: toxicokinetic investigations in a unilateral nasal occlusion model. Toxicol Appl Pharmacol 169:238-248.

Calne DB, 1983. Aetiology of Parkinson's disease. Lancet, December 24/31, pp. 1457-1459.

Calne DB, Chu NS, Huang CC et al., 1994. Manganism and idiopathic parkinsonism: similarities and differences. Neurology 44:1583-1586.

Chandra SV and Tandon SK, 1973. Enhanced manganese toxicity in iron-deficient rats, Environ Physiol Biochem 3:230-235.

Chandra SV, Shukla GS and Srivastava RS, 1981. An exploratory study of manganese exposure to welders. Clin Toxicol 18:407-416.

Cheong HK, Cho S, Kim KS, Jin Y, Kim E, Kang SK and Kim Y, 2002. High signal intensity on magnetic resonance imaging as a predictor of neurobehavioral performance of workers exposed to manganese. 8th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002. Abstract Book p. 113.

Chia SE, Foo SC, Gan SL, Jeyaratnam J and Tian C, 1993a. Neurobehavioral functions among workers exposed to manganese ore. Scand J Work Environ Health 19:264-270.

Chia S, Goh J, Lee G, Foo S, Gan S, Bose K and Jeyaratnam J, 1993b. Use of a computerized postural sway measurement system for assessing workers exposed to manganese. Clin Exp Pharmacol Physiol 20:549-553.

Chia SE, Gan SL, Chua LH et al., 1995. Postural stability among manganese exposed workers. Neurotoxicology 16:519-526.

Chu NS, Hochberg FH, Calne DB et al., 1995. Neurotoxicity of manganese. In: Chang L, Dyyer R, eds. Handbook of Neurotoxicology. New York, NY: Marcel Dekker, Inc., 91-103.

*CICADS, 1999. World Health Organization, Manganese and its compounds, consulted March 26, 2002, http://www.inchem.org/documents/cicads/cicads/cicad12.htm.

Cook DG, Fahn S and Brait KA, 1974. Chronic manganese intoxication. Arch Neurol 30:59-64.

Cooper WC, 1984. The health implications of increased manganese in the environment resulting from the combustion of fuel additives: a review of the literature. J Toxicol Environ Health 14:23-46.

Cotzias GC, Miller ST, Papavasiliou PS and Tang LC, 1976. Interactions between manganese and brain dopamine. Med Clin North Am 60:729-738.

Davidsson L, Cederblad A, Hagebo E et al., 1988. Intrinsic and extrinsic labeling for studies of manganese absorption in humans. J Nutr 118:1517-1524.

Davidsson L, Cederblad A, Lönnerdal B et al., 1989a. Manganese retention in man: a method for estimating manganese absorption in man. Am J Clin Nutr 49:170-179.

Davidsson L, Cederblad A, Lönnerdal B et al., 1989b. Manganese absorption from human milk, cow's milk, and infant formulas in humans. Am J Dis Child 143:823-827.

Davis CD and Greger JL, 1992. Longitudinal changes of manganese-dependent superoxide dismutase and other indices of manganese and iron status in women. Am J Clin Nutr 55:747-752.

Davis CD, Malecki EA and Greger JL, 1992a. Interactions among dietary manganese, heme iron and non-heme iron in women. Am J Clin Nutr 56:926-932.

Davis CD, Wolf TL and Greger JL, 1992b. Varying levels of manganese and iron affect absorption and gut endogenous losses of manganese by rats. J Nutr 122:1300-1308.

Devenyi AG, Barron TF and Mamourian AC, 1994. Dystonia, hyperintense basal ganglia, and whole blood manganese levels in Alagille's syndrome. Gastroenterology 106:1068-1071.

DFG 2000. Deutsche Forchungsgemeinschaft. List of Mak and Bat values 2000. Maximum concentrations and biological tolerance values at the workplace. Commission of the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 36. Weinheim, Germany: Wiley-Verlag GmBH, VCH, 72.

Dietz MC, Ihrig A, Wrazidlo W, Bader M, Jansen O, Triebis G, 2001. Results of magnetic resonance imaging in long term manganese dioxide-exposed workers. Environ Res 85:37-40.

Diez-Ewald M, Weintraub LR and Crosby WH, 1968. Interrelationship of iron and manganese metabolism. Proc Soc Exp Biol Med 129:448-451.

Di Monte DD, Lavasani M, Manning-Bog AB, 2002. Environmental factors in Parkinson's disease. Neurotoxicology 23:487-502.

Discalzi G, Pira E, Hernandez EH, Valentini C, Turbiglio M, Meliga F, 2000. Occupational Mn parkinsonism: magnetic resonance imaging and clinical patterns following $CaNa_2EDTA$ chelation. Neurotoxicology 21:863-866.

Doisy EA, 1973. Effects of deficiency in manganese upon plasma levels of clotting proteins and cholesterol in man. Trace Element Metabolism. In: Animals-2, 2nd ed., (WG Hoekstra, JW Suttie, AE Ganther, W Mertz, eds.) University Park Press, Baltimore, pp. 668-670.

Donaldson J, McGregor D and LaBella F, 1982. Manganese neurotoxicity: a model for free radical mediated neurodegeneration? Can J Physiol Pharmacol 60:1398-1405.

Dorman DC, Struve MF and Wong BA, 2001. Pharmocokinetic factors that influence manganese delivery to the brain. CIIT Activities, 21(7-8):1-8.

Dorman DC, Brenneman KA, McElveen AM, Lynch SE, Roberts KC, Wong BA, 2002. Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. J Toxicol Environ Health 65:1493-1511.

Dorman DC and Struve MF, 2002. Manganese neurotoxicity: insights gained from experimental animal studies. 8th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002. Abstract Book p. 98.

Drown DB, Oberg SG and Sharma RP, 1986. Pulmonary clearance of soluble and insoluble forms of manganese. J Toxicol Environ Health 17:201-212.

Eckel WP and Langley WD, 1988. A background-based ranking technique for assessment of elemental enrichment in soils at hazardous waste sites. In: Superfund '88: Proceedings of the 9th National Conference. Washington, DC, 282-286.

Ejima A, Imamura T, Nakamura S et al., 1992. Manganese intoxication during total parenteral nutrition [letter]. Lancet 339:426.

Ellenhorn MJ and Barceloux DG, 1988. Medical toxicology: diagnosis and treatment of human poisoning. New York, NY: Elsevier, 1047-1048.

Emara AM, El-Ghawabi SH, Madkour OI et al., 1971. Chronic manganese poisoning in the dry battery industry. Br J Ind Med 28:78-82.

Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth Jr WT, Scott KC, Hudnell K, Anger WK and Camicioli R, 2001. Parkinsonism and occupational exposure to pesticides. Occup Environ Med 58:582-589.

EPA, 1978. U.S. Environmental Protection Agency. Federal Register 43:41424-41429.

EPA, 1979. U.S. Environmental Protection Agency. Federal Register 44:58952-58965.

EPA, 1981. U.S. Environmental Protection Agency. Federal Register 46:58360.

EPA. 1983. Human exposure to atmospheric concentrations of selected chemicals. Vol. II. Report to U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC, by Systems Applications, Incorporated, San Rafael, CA. NTIS No. PB83-265249.

EPA, 1984a. Health assessment document for manganese. Final draft. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/8-83-013F.

EPA, 1984b. Health effects assessment for manganese (and compounds). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA/540/1-86/057.

EPA, 1985a. Chemical identity—manganese tricarbonyl methylcyclopentadienyl. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Toxic Substances.

EPA, 1985b. Locating and emitting air emissions from sources of manganese. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/4-84-007h.

EPA, 1985c. U.S. Environmental Protection Agency. Federal Register 50:32627-32628.

EPA, 1987. Toxic air pollutant/source crosswalk: a screening tool for locating possible sources emitting toxic air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA-450/4-87-023a.

EPA, 1993. Drinking water criteria document for manganese. Environmental Protection Agency, Office of Health and Environmental Assessment, Cincinnati, OH.

EPA, 1995a. U.S. Environmental Protection Agency. Federal Register 60:36414.

EPA, 1995b. Proceedings: Workshop on the bioavailability and oral toxicity of manganese. Environmental Criteria and Assessment Office, Office of Research and Development, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. Washington D.C.

EPA, 1995c. Integrated Risk Information System (IRIS). *Health Risk Assessment for Manganese*, on line, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Eriksson H, Magiste K, Plantin LO et al., 1987. Effects of manganese oxide on monkeys as revealed by a combined neurochemical, histological and neurophysiological evaluation. Arch Toxicol 61:46-52.

Eriksson H, Tedroff J, Thuomas KA et al., 1992. Manganese induced brain lesions in Macaca fascicularis as revealed by positron emission tomography and magnetic resonance imaging. Arch Toxicol 66:403-407.

Fairhall LT, 1957. Industrial Toxicology, Baltimore, Williams & Wilkins, p.74.

Fechter LD, Johnson DL, Lynch RA, 2002. The relationship of particle size to olfactory nerve uptake of a non-soluble form of manganese into brain. Neurotoxicology 23: 177-183.

Feldman RG, 1999. Occupational and environmental Neurotoxicology, Chapter 10: Manganese. Philadelphia, PA: Lippincott-Raven Publishers, 166-168.

Fell JM, Reynolds AP, Meadows N et al., 1996. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet 347:1218-1221.

Fitzgerald K, Mikalunas V, Rubin H, McCarthey R, Vanagunas A and Craig RM, 1999. Hypermanganesemia in patients receiving total parenteral nutrition. J Parenter Enteral Nutr 23:333-6.

Flinn RH, Neal PA, Reinhart WH et al. (1990), Chronic manganese poisoning in an ore-crushing mill. U.S. Public Health Services Bull. No. 247. USPHS.

*Francis AA and Forsyth C, 1995. Toxicity summary for manganese. Oak Ridge Reservation Environmental Restoration Program, prepared for the US Department of Energy, July 1995.

Freeland-Graves JH, Bales CW and Behmardi F, 1987. Manganese requirements of humans. In: Kies C, ed. Nutritional bioavailability of manganese. Washington, DC, American Chemical Society.

Freeland-Graves J and Llanes C, 1994. Models to study manganese deficiency. In: Klimis-Tavantzis DJ, ed. Manganese in health and disease. Boca Raton, FL, CRC Press, pp. 59-86.

Friedman BJ, Freeland-Graves JH, Bales CW et al., 1987. Manganese balance and clinical observations in young men fed a manganese-deficient diet. J Nutr 117:133-143.

Gasparotti R, Liserre R, Benedetti L, Mariotti O, Lucchini R and Puoti M, 2002. Use of brain MRI in manganese exposure. 8th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002. Abstract Book p. 54.

Gennart JP, Buchet JP, Roels H et al., 1992. Fertility of male workers exposed to cadmium, lead, or manganese. Am J Epidemiol 135:1208-1219.

Gibbs JP, Crump KS, Houck DP et al., 1999. Focused medical surveillance: a search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust. Neurotoxicology 20:299-314.

Goldsmith JR, Herishanu Y, Abarbanel JM and Wembaurn Z,1990. Clustering of Parkinson's disease points to environmental etiology. Arch Environ Health 45:88-94.

Greger JL, Davis CD, Suttie JW, and Lyle BJ, 1990. Intake, serum concentrations and urinary excretion of manganese by adult males. Am J Clin Nutr 54:457-461.

Greger JL, 1998. Dietary standards for manganese: overlap between nutritional and toxicological studies. J Nutr 128(2 Suppl):368S-371S.

Greger JL, 1999. Nutrition versus toxicology of manganese in humans: evaluation of potential biomarkers. Neurotoxicology 20:205-212.

Gupta SK, Murthy RC and Chandra SV, 1980. Neuromelanin in manganese-exposed primates. Toxicol Lett 6:17-20.

Haddad LM and Winchester JF, 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1031.

Hauser RA, Zesiewicz TA, Martinez C et al., 1996. Blood manganese correlates with brain magnetic resonance imaging changes in patients with liver disease. Can J Neurol Sci 23:95-98.

Henricksson and Tjalve H, 2000. Manganese taken up into the CNS via the olfactory pathway in rats affects astrocytes. Toxicol Sci 55:392-398.

Hernandez EH, Discalzi G, Jarre L and Dassi P, 2002. Manganese intoxication the cause of inexplicable epileptic seizures in a 3 years old child. 8th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002. Abstract Book p.147.

Hertzman C, Wiens M, Bowering D, Snow B and Calne DB, 1990. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med 17:349-355.

Hochberg F, Miller G, Valenzuela R, McNelis S, Crump KS, Covington T, Valdivia G, Hochberg B and Trustman JW, 1996. Late motor deficits of Chilean manganese miners: a blinded control study. Neurology 47:788-795.

HSDB, 1993. Hazardous Substances Data Bank. Bethesda, MD: National Institutes of Health, National Library of Medicine.

*HSDB, 2001. Hazardous Substances Data Bank. Bethesda, MD: National Institutes of Health, National Library of Medicine.

Huang CC, Chu NS, Lu CS et al., 1989. Chronic manganese intoxication. Arch Neurol 46:1104-1106.

Huang CC, Chu NS, Lu CS et al., 1993. Progression after chronic manganese exposure. Neurotoxicology 43:1479-1483.

Huang CC, Chu NS, Lu CS et al., 1998. Long-term progression in chronic manganism. Ten years of follow-up. Neurology 50:698-700.

Hurley LS and Keen CL, 1987. Manganese. In: Trace elements in human and animal nutrition, Fifth Ed., Vol. 1 (W Mertz, ed.) San Diego, Academic Press Inc., pp. 185-223.

*Inoue N and Makita Y, 1996. Neurological aspects in human exposure to manganese, published in “Toxicology of Metals”, CRC Handbook, edited by Louis W. Chang, Lewis Publishers, New York, p.415-421.

Iregren A, 1990. Psychological test performance in foundry workers exposed to low levels of manganese. Neurotoxicol Teratol 12:673-675.

Iregren A, 1992. Psychological testing for neurotoxic effect from manganese in active workers. Symposium on Manganese Toxicity, Proceedings International Manganese Institute, Paris (November 19-20, 1992).
*Iregren A. 1999. Manganese neurotoxicity in industrial exposures: proof of effects, critical exposure level, and sensitive tests. Neurotoxicology 20:315-324.

*IRIS, 1998. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. May 11, 1998.

Jarvisalo J, Olkinuora M, Kiilunen M et al., 1992. Urinary and blood manganese in occupationally nonexposed populations and in manual metal arc welders of mild steel. Int Arch Occup Environ Health 63:495-501.

*Jiang Y, Lu J, Xie P, et al., 1996. Effects of manganese on the sexual function and reproductive outcome of male exposed workers. Chi J Ind Hyg Occup Dis 14:271-273. (Chinese), cited in ATSDR 2000.

Keen CL and Leach RM, 1988. Manganese, In: *Handbook on Toxicity of Inorganic Compounds*, H.G. Seiler and H. Sigel eds., New York, Marcel Dekker Inc., pp. 405-415.

Keen CL, Zidenberg-Cher S, 1990. Manganese. In: Brown M, ed. Present knowledge in nutrition, sixth edition. Washington, DC: International Life Sciences Institute Nutrition Foundation, 279-286.

Kim Y, Kim KS, Yang JS, Park IJ, Kim E, Jin Y, Kwon KR, Chang KH, Kim JW, Park SH, Lim HS, Cheong HK, Shin YC, Park J and Moon Y, 1999. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology. 20:901-907.

Komaki H, Maisawa S, Sugai K, Kobayaski Y and Hashimoto T, 1999. Tremor and seizures associated with chronic manganese intoxication. Brain Dev 21:122-24.

Krieger D, Krieger S, Jansen O, Gass P, Theilmann L and Lichtnecker H, 1995. Manganese and chronic hepatic encephalopathy. Lancet 346: 270-274.

Ky S, Deng H, Xie P and Hu W, 1992. A report of two chronic cases of serious manganese poisoning treated with sodium para-aminosalicylic acid. Br J Ind Med 49:66-69.

Lauwerys R, Roels H, Genet P et al., 1985. Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. Am J Ind Med 7:171-176.

Lauwerys RR, Bernard A, Roels H et al., 1992. Health risk assessment of long term exposure to chemicals: application to cadmium and manganese. Arch Toxicol Suppl 15:97-102.

Lauwerys R, 1999. Toxicologie industrielle et intoxications professionnelles, 4^{e} Édition. Masson, Paris.

Lioy PJ, 1983. Air pollution emission profiles of toxic and trace elements from energy related sources: status and needs. Neurotoxicology:103-112.

Lloyd Davies TA ., 1946. Manganese pneumonitis. Br J Ind Med 3:111-135.

Loranger S and Zayed J, 1997a. Environmental contamination and human exposure to airborne total and respirable manganese in Montreal. J Air Waste Manag Assoc 47:983-989.

Loranger S and Zayed J, 1997b. Environmental contamination and human exposure assessment to manganese in the St.Lawrence River ecozone (Quebec, Canada) using an environmental fate/exposure model: Geotox. SAR QSAR. Environ Res 6:105-19.

Lu CS, Huang CC, Chu NS and Calne DB, 1994. Levodopa failure in chronic manganism. Neurology. 44:1600-1602.

Lucchini R, 1992. Neurobehavioral effects in a ferromanganese group of workers after temporary cessation of exposure. Symposium on Manganese Toxicity, Proceedings. International Manganese Institute, Paris (November 19-20, 1992)

Lucchini R, Selis L, Folli D et al., 1995. Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure. Scand J Work Environ Health 21:143-149.

Lucchini R, Apostoli P, Perrone C et al., 1999. Long term exposure to “low levels” of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology 20:287-298.

*Luccini R, Albini E, Placidi D, Gasparotti R, Pizolli MG, Montani G, Allesio L, 2000. Brain magnetic resonance imaging and manganese exposure. Neurotoxicology 21:769-775.

Lundberg P, 1997. Scientific Basis for Swedish Occupational Standards XVIII, National Institute for Working Life, Arbete Och Halsa 25:32-44.

Lydén A, Larsson B and Lindquist NG, 1984. Melanin affinity of manganese. Acta Pharmacol Toxicol (Copenh) 55:133-138.

Mena I, Marin O, Fuenzalida S et al., 1967. Chronic manganese poisoning: clinical picture and manganese turnover. Neurology 17:128-136.

Mena I, Horiuchi K, Burke K et al., 1969. Chronic manganese poisoning: individual susceptibility and absorption of iron. Neurology 19:1000-1006.

Mergler D, 1992. Early nervous system dysfunction among Canadian workers in a ferro-and silico-manganese alloy plant. Symposium on Manganese Toxicity, Proceedings. International Manganese Institute, Paris (November 18-20, 1992).

Mergler D, Huel G, Bowler R et al., 1994. Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res 64:151-180.

Mergler D, 1996. Manganese: the controversial metal: at what levels can deleterious effects occur? Can J Neuro Sci. 23:93-94.

* Mergler D and Baldwin M, 1997. Early manifestations of manganese neurotoxicity in humans: an update. Environmental research, 78(1-2):92-100.

Mergler D, Baldwin M, Bélanger S et al., 1999. Manganese neurotoxicity, a continuum of dysfunction: Results from a community based study. Neurotoxicology 20:327-342.

Minoia C, Sabbioni E, Apostoli P et al., 1990. Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. Sci Total Environ 95:89-105.

Morrow P, 1970. Retention rate of inhaled submicron manganese dioxide. In : Inhaled Particles III, Vol. II. WH Walton, ed. Old Working, Surrey, U.K. Unwin Bros., Ltd., Gresham Press.

Nelson K, Golnick J, Korn T et al., 1993. Manganese encephalopathy: utility of early magnetic resonance imaging. Br J Ind Med 50:510-513.

Newland MC, Cox C, Hamada R et al., 1987. The clearance of manganese chloride in the primate. Fundam Appl Toxicol 9:314-328.

Newland MC, Ceckler TL, Kordower JH et al., 1989. Visualizing manganese in the primate basal ganglia with magnetic resonance imaging. Exp Neurology 106:251-258.

Newland MC and Weiss B, 1992. Persistent effects of manganese on effortful responding and their relationship to manganese accumulation in the primate globus pallidus. Toxicol Appl Pharmacol 113:87- 97.

NIOSH, 1997. NIOSH/OSHA Pocket Guide To Chemical Hazards. US Department of Health and Human Services.

Normandin L, Carrier G, Gardiner PF, Kennedy G, Hazell AS, Mergler D, Butterworth RF, Philippe S, Zayed J, 2002. Assessment of bioaccumulation, neuropathology and neurobehavioral following subchronic (90 days) inhalation in Sprague-Dawley rats exposed to manganese phosphate. Toxicol Appl Pharmacol 183:135-145.

Normandin L, 2002. Évaluation de la bioaccumulation, de la neurohistopathologie et des effets neurocomportementaux associés à une exposition subchronique (90 jours) par inhalation au phosphate de manganèse, thèse de doctorat, Université de Montréal, sous presse.

NRC, 1989. Recommended dietary allowances. Washington, DC: National Research Council. Tenth Edition, 231-235.

* NTP, 1993. Toxicology and carcinogenesis studies of manganese (II) sulfate monohydrate in F344/N rats and B6C3F1 mice (feed study). National Toxicology Program. Technical Report Series 428. Riskline 94030007.

Oberdoerster G and Cherian G, 1988. Proceedings, 17th Rochester International. Conf. Environ. Toxicol. Biological Monitoring of Toxic Metals. TW Clarkson ed., New York, Plenum Press.

Olanow CW, Good PF, Shinotoh H et al., 1996. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 46:492-498.

Ono J, Harada K and Kodaka R, 1995. Manganese deposition in the brain during long-term total parenteral nutrition. J Parent Enter Nutr 19:310-312.

OSHA, 1998. Occupational Safety and Health Administration. Code of Federal Regulations 29 CFR 1910.1000. Table Z-1. Limits for air contaminants.

OTA, 1990. Neurotoxicology: identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment, OTA-BA-438.

* Pal PK, Samii A and Calne DB, 1999. Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology 20:227-238.

Pomier-Layrargues G, Spahr L and Butterworth RF, 1995. [lettre]. Lancet 345:735.

Pomier-Layrargues G, Rose C, Spahr L et al., 1998. Role of manganese in the pathogenesis of portalsystemic encephalopathy. Metabol Brain Dis 13:311-317.

Proctor NH, Hughes JP and Fischman ML, 1988. Chemical hazards of the workplace, 2nd ed. Philadelphia, PA: J.B. Lippincott Company, 307-308.

* RAIS, Risk Assessment Information System, Toxicity Summary for Manganese, consulted April 19, 2002, http://rais.ornl.gov/tox/profiles/mn.sheml.

Rehnberg GL, Hein JF, Carter SD et al., 1980. Chronic manganese oxide administration to pre-weanling rats: manganese accumulation and distribution. J Toxicol Environ Health 6:217-226.

Rehnberg GL, Hein JF, Carter SD et al., 1981. Chronic ingestion of Mn_3O_4 by young rats: tissue accumulation, distribution, and depletion. J Toxicol Environ Health 7:263-272.

Rehnberg GL, Hein JF, Carter SD et al., 1982. Chronic ingestion of Mn_30_4 by rats: tissue accumulation and distribution of manganese in two generations. J Toxicol Environ Health 9:175-188.

Rodier J, 1955. Manganese poisoning in Moroccan miners. Br J Ind Med 12:21-35.

Roels H, Sarhan MJ, Hanotiau I, de Fays M, Genet P, Bernard A, Buchet JP, Lauwerys R, 1985. Preclinical toxic effects of manganese in workers from a Mn salts and oxides producing plant. Sci Total Environ 42:201-206.

Roels H, Lauwerys R, Buchet JP et al., 1987a. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. Am J Ind Med 11:307- 327. [Erratum 1987. Am J Ind Med 12:119-120].

Roels H, Lauwerys R, Genet P et al., 1987b. Relationship between external and internal parameters of exposure to manganese in workers from a manganese oxide and salt producing plant. Am J Ind Med 11:297-305.

Roels H and Lauwerys R, 1992. Health risk assessment of chronic exposure to MnO_2 dust. An epidemiological study in a battery plant. Symposium on Manganese Toxicity, Proceedings. International Manganese Institute, Paris (November 19-20, 1992).

Roels HA, Ghyselen P, Buchet JP et al., 1992. Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49:25-34.

Roels H, Meiers G, Delos M et al., 1997. Influence of the route of administration and the chemical form ($MnCl_2$, MnO_2) on the absorption and cerebral distribution of manganese in rats. Arch Toxicol 71:223-230.

Roels HA, Ortega Eslava MI, Ceulemans E et al., 1999. Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. Neurotoxicology 20:255-272.

Roels HA, 2002. Translation of evidence about occupational exposure to manganese into strategies of prevention, 8th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health, Brescia, Italy, June 23-26, 2002. Abstract Book p. 97.

Rope SK, Arthur WJ, Craig TH et al., 1988. Nutrient and trace elements in soil and desert vegetation of southern Idaho. Environ Monitor and Assess 10:1-24.

Rose C, Butterworth RF, Zayed J et al., 1999. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 117:640-644.

Rosenstock HA, Simons DG and Meyer JS, 1971. Chronic manganism: neurologic and laboratory studies during treatment with levodopa. J Am Med Assoc 217:1354-1358.

RSST, 2001. Règlement sur la santé et sécurité du travail, Décret 885-2001. Gazette officielle du Québec, 3e trimestre 2001. (Regulation respecting occupational health and safety)

Saric M, Lucic-Palaic, 1977. Possible synergism of exposure to airborne manganese and smoking habit in the occurrence of respiratory symptoms. In: Walton WH, ed. Inhaled Particles. IV. New York, NY: Pergamon Press, 773-779.

Schroeder HA, Balassa JJ and Tipton IH, 1966. Essential trace metals in man: manganese. A study in homeostasis. J Chron Dis 19:545-571.

Schroeder WH, Dobson M, Kane DM et al., 1987. Toxic trace elements associated with airborne particulate matter: a review. J Air Pollut Control Assoc 37:1267-1285.

Schuler P, Oyanguren H, Maturana V et al., 1957. Manganese poisoning: environmental and medical study at a Chilean mine. Ind Med Surg 26:167-173.

Segura-Aguilar J and Lind C., 1989. On the mechanism of the Mn^{+3} – induced neurotoxicity of dopamine: prevention of quinone-derived oxygen toxicity by DT diaphorase and superoxide dismutase. Chem Biol Interact 72:309-324.

Semchuck KM, Love EJ and Lee RG. 1992. Parkinson's disease and exposure to agricultural work and pesticide. Neurology 42:1328-1335.

Shinotoh H, Snow BJ, Hewitt KA, Pate BD, Doudet D, Nugent R, Perl DP, Olanow W and Calne DB, 1995. MRI and PET studies of manganese-intoxicated monkeys. Neurology. 45:1199-1204.

Siqueira ME, Hirata MH and Adballa DS, 1991. Studies on some biochemical parameters in human manganese exposure. Med Lav 82:504-509.

Sjögren B, Gustavsson P and Hogstedt C, 1990. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. Br J Ind Med 47:704-707.

Sjögren B, Iregren A, Frech W, Hagman M, Johansson L, Tesarz M and Wennberg A, 1996. Effects on the nervous system among welders exposed to aluminum and manganese. Occup Environ Med 53:32-40.

Smargiassi A and Mutti A, 1999. Peripheral biomarkers of exposure to manganese. Neurotoxicology 20:401-406.

Smith MO, Sherman IL, Miller LC, Robbins KR and Halley JT, 1995. Relative biological availability of manganese from manganese proteinate, manganese sulfate, and manganese monoxide in broilers reared at elevated temperatures. Poultry Sci 74:702-707.

Smyth LT, Ruhf RC, Whitman NE and Dugan T, 1973. Clinical manganism and exposure to manganese in the production and processing of ferromanganese alloy. J Occup Med 15:101-109.

Spahr L, Butterworth RF, Fontaine S et al., 1996. Increased blood manganese in cirrhotic patients: relationship to pallidal magnetic resonance signal hyperintensity and neurological symptoms. Hepatology 24:1116-1120.

Stokinger, HE, 1981. The Metals, In: *Patty's Industrial Hygiene and Toxicology*, Vol 2A, eds. GD Clayton and FE Clayton, New York, John Wiley & Sons, 1749-1769.

Sumino K, Hayakawa K, Shibata T et al., 1975. Heavy metals in normal Japanese tissues: amounts of 15 heavy metals in 30 subjects. Arch Environ Health 30:487-494.

Tanaka S and Lieben J, 1969. Manganese poisoning and exposure in Pennsylvania. Arch Environ Health 19:674-684.

Tanaka S, 1994. Manganese and its compounds. In: Zenz C, Dickerson OB, Horvath EP, eds. Occupational Medicine. 3rd Edition. St. Louis, MO: Mosby, 542-548.

Tjälve H, Henriksson J, Tallkvist J et al., 1996. Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. Pharmacol Toxicol 79:347-356.

*Tjälve H and Henriksson J, 1999. Uptake of metals in the brain via olfactory pathways. Neurotoxicology 20:181-195.

Valentin H, Schiele R. 1983. Manganese. In: Alessio L, et al. Human biological monitoring of industrial chemicals series. Luxembourg: Commission of the European Communities. EUR-8476-EN.

Verity MA, 1999. Manganese toxicity: a mechanistic hypothesis. Neurotoxicology 20:489-498.

Vitarella D, Wong BA, Moss OR, Dorman DC, 2000. Pharmacokinetics of inhaled manganese phosphate in male Sprague-Dawley rats following subacute (14 days) exposure. Toxicol Appl Pharmacol 163:279-285.

Wedler FC, 1994. Biochemical and nutritional role of manganese: an overview. In: Klimis-Tavantzis DJ, ed. Manganese in Health and Disease. Boca Raton, LA: CRC Press, 1-36.

Wennberg A, Iregren A, Struwe G et al., 1991. Manganese exposure in steel smelters: a health hazard to the nervous system. Scand J Work Environ Health 17:255-262.

Whitlock CM, Amuso SJ and Bittenbender JB, 1966. Chronic neurological disease in two manganese steel workers. Am Ind Hyg Assoc J 27:454-459.

*WHO, 1981. Environmental health criteria 17: Manganese. World Health Organization, Geneva, Switzerland.

*WHO, 1986. Diseases caused by manganese and its toxic compounds. Early detection of occupational diseases, World Health Organization, Geneva, Switzerland, 69-73.

*WHO, 1987. Manganese. In: Air quality guidelines for Europe. European Series No. 23. Copenhagen, Denmark: World Health Organization Regional Office for Europe, 262-271.

*WHO, 1997. Manganese. In: Air quality guidelines for Europe, 2nd Edition. World Health Organization, Regional Office for Europe, Copenhagen, WHO Regional Publications, European Series. Internet address: http://www.who.int/peh/air/airguides2.htm. Accessed November 11, 1999.

*WHO, 1999. Air quality guidelines for Europe, 2nd ed. Copenhagen, World Health Organization Regional Office for Europe.

*WHO, 2001. Air quality guidelines for Europe, Manganese, Chapter 6.8, World Health Organization Regional Office for Europe, Copenhagen Denmark.

Wolters EC, Huang CC, Clark C et al., 1989. Positron emission tomography in manganese intoxication. Ann Neurol 26:647-651.

Yamada M, Ohno S, Okayasu I et al., 1986. Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. Acta Neuropathol (Berl) 70:273-278.

Yiin SJ, Lin TH and Shih TS, 1996. Lipid peroxidation in workers exposed to manganese. Scand J Work Environ Health 22:381-386.

Zayed J, Thibault C, Gareau L et al., 1999a. Airborne manganese particulates and methylcyclopentadienyl manganese tricarbonyl (MMT) at selected outdoor sites in Montreal. Neurotoxicology 20:151-157.

Zayed J, Vyskocil A and Kennedy G, 1999b. Environmental contamination and human exposure to manganese: contribution of methylcyclopentadienyl manganese tricarbonyl in unleaded gasoline. Int Arch Occup Environ Health 72:7-13.

Zuber M and Alperovitch A, (1991). Maladie de Parkinson et facteurs environmentaux Rev Epidémiol Santé Publique 39:373-387.