Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for manganese and inorganic manganese compounds

SCOEL/SUM/127
June 2011

European Commission

Table of Contents

Recommendation from the Scientific Committee on Occupational Exposure Limits for Manganese and inorganic manganese compounds

8 hour TWA:	0.200 mg/m³ (inhalable fraction)
	0.050 mg/m³ (respirable fraction)
STEL (15 mins):	not assigned
Biological Limit Value:	not assigned (*see page 17*)
Notation:	none

Substance Identity and Properties

Table 1 - Names, synonyms, formulae and mass of manganese and some commonly used manganese compounds

Substance	Synonyms	Formula	Atomic/molecular weight
Manganese		Mn	54.94
Manganese (IV) dioxide	Manganese (IV) oxide, manganic oxide, pyrolusite.	MnO_2	86.94
Manganese (II) oxide	Manganese (II) oxide, manganous oxide, manganosite, manganese green	MnO	70.94
Manganese (II,III) oxide	Manganomanganic oxide, hausmannite	Mn_3O_4	228.81
Manganese (II) sulphate	Manganese sulphate, manganous sulphate, sulphuric acid–manganese salt	$MnSO_4$	151
Potassium permanganate	1. Permanganic acid – potassium salt, chameleon mineral, Condy's crystals	$KMnO_4$	158.04
Manganese (II) carbonate	Manganous carbonate, rhodochrosite	$MnCO_3$	114.95
Manganese (III) fluoride		MnF_3	111.93
Manganese (II) dichloride tetrahydrate	Manganous chloride tetra-hydrate	$MnCl_24H_2O$	197.91
Manganese (II) sulphide	Manganese monosulphide, alabandite, manganblende	MnS	87
Manganese (II) nitrate	Manganous nitrate	$Mn(NO_3)_2$	178.95

Table 2 - CAS and EINECS numbers for manganese and some commonly used manganese compounds

Substance	CAS no	EINECS no
Manganese	7439–96–5	231–105–1
Manganese (IV) dioxide	1313–13–9	215–206–6
Manganese (II) oxide	1344–43–0	215–695–8
Manganese (II,III) oxide	1317–35–7	215–266–5
Manganese (II) sulphate	7785–87–7	232–089–9
Potassium permanganate	7722–64–7	231–760–3
Manganese (II) carbonate	598–62–9	209–942–9
Manganese (III) fluoride	7783–53–1	232–006–6
Manganese (II) dichloride tetrahydrate	13446–34–9	231–869–6
Manganese (II) sulphide	18820–29–-6	242–599–3
Manganese (II) nitrate	15710–66–4	

Table 3 - Labelling phrases applicable to manganese and manganese compounds*

Substance	European Union risk phrases	European Union safety phrases
Manganese	Not classified.	Not classified
Manganese (VI) dioxide	R48/20 Harmful: danger of serious damage to health by prolonged exposure through inhalation R20/22: Harmful by inhalation and if swallowed	S2: Keep out of reach of children S22: Do not breathe dust. S36: Wear suitable protective clothing
Manganese (II) oxide	Not classified	Not classified
Manganese (II,III) oxide	Not classified	Not classified
Manganese (II) sulphate (as hydrate)	R48/20: Harmful: danger of serious damage to health by prolonged exposure through inhalation R41 Irritant; Risk of serious damage to eyes. R51/53 Dangerous for the environment; Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	S22: Do not breathe dust. S2: Keep out of reach of children S26: In case of contact with eyes, rinse immediately with plenty of water & seek medical advice. S39: Wear face/eye protection S61: Avoid release to the environment. Refer to special instructions/SDS S60: This material and its container most be disposed of as hazardous waste
Potassium permanganate	R8–22 Contact with combustible material may cause fire. Harmful if swallowed.	S17–45–26–36/37/39 Keep away from combustible material. In case of accident or if you feel unwell, seek medical advice (show the label where possible). In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing, gloves and eye/face protection.
Manganese (III) fluoride	R8 R20/21/22 R36/67/68 Contact with combustible material may cause fire. Harmful by inhalation, contact with the skin or if swallowed. Irritating to eyes, respiratory system and skin.	S17 S26 S36, S37S39 Keep away from combustible material. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing. Wear suitable gloves. Wear eye/face protection.
Manganese (II) dichloride tetrahydrate	R48/20: Harmful: danger of serious damage to health by prolonged exposure through inhalation R51/53 Dangerous for the environment; Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment	S22: Do not breathe dust. S39: Wear face/eye protection S61: Avoid release to the environment. Refer to special instructions/SDS S60: This material and its container most be disposed of as hazardous waste

Manganese sulphide	R36/37: Irritating to the eyes and the respiratory system R43: May cause sensitisation by skin contact R52/53: Harmful to aquatic organisms may cause long term effects in the aquatic environment.	S22: Do not breath dust S36: Wear suitable protective clothing S61: Avoid release to the environment. Refer to special instructions/SDS S60: This material and its container most be disposed of as hazardous waste
Manganese (II) nitrate	R8: Contact with combustible material may cause fire. R22: Harmful if swallowed R48/20: Harmful: danger of serious damage to health by prolonged exposure through inhalation R34: Corrosive, causes burns R52/53: Harmful to aquatic organisms may cause long term effects in the aquatic environment.	S7/8: Keep container tightly closed and dry S17: Keep away from combustible materials S26: In case of contact with eyes rinse immediately with plenty of water and seek medical advice S28: After contact with skin wash immediately with plenty of water S29/56: Do not empty into drains, dispose of this material and its container at hazardous or special waste collection points S36/37/S39: Wear suitable protective clothing, gloves and eye/face protection S62: If swallowed, do not induce vomiting, seek medical advice immediately and show this container and label S61: Avoid release to the environment. Refer to special instructions/SDS S60: This material and its container most be disposed of as hazardous waste

* H and R phrases are used for classified compounds according to CLP and DSD respectively. H and R phrases are normally supported by Precautionary statements (P) and safety phrases (S) according to CLP and DSD respectively.

Table 4 - Physicochemical data and properties of manganese and manganese compounds used in industry

Substance	Description	Melting Pt °C	Boiling Pt °C	Density	Solubility
Manganese	Silvery grey solid	1260	2097	7.2	Decomposes in water
Manganese (IV) dioxide	Black solid	Decomposes at 535	Not applicable	5.10	Insoluble
Manganese (II) oxide	Grey green – dark green solid	1785	Decomposes at 1840	5.37	Insoluble
Manganese (II,III) oxide	Brownish black	940	Decomposes at 1040	5.00	Negligible

Manganese (II) sulphide	Polymorph – red Polymorph – green Polymorph – red	1610		4.00	Soluble in hydrochloric acid
Manganese (II) sulphate	Reddish solid	700	Decomposes at 850	3.25	520g/ℓ
Potassium permanganate	Purple crystalline solid	Decomposes at <240	Not applicable	2.7	63.8g/ℓ
Manganese (II) carbonate	Pink to white powder with almost no odour	Decomposes at >200	Not applicable	3.7	Less than 0.1%
Manganese (III) fluoride	Purple powder or crystals	Decomposes at >600	Not applicable	3.54	
Manganese (II) dichloride tetrahydrate	Rose coloured crystals	122 (Dehydrates at 55)		1.913	Soluble
Manganese (II) nitrate hydrate	Pink diamond shaped crystals	25.8	129.5	1.54	Soluble in water and alcohol

1. Occurrence and Use

Manganese (Mn) is a Group VIIb transition metal, which exists in several oxidation states (II, III, IV, VI and VII) and forms a range of inorganic and organometallic compounds. This assessment considers only the inorganic forms of the element.

Manganese occurs naturally, most commonly as oxides and as sulphide, carbonate and silicate. It occurs in most iron ores. Most manganese (II) compounds are water-soluble. Manganese is used in the production of ferrous and non-ferrous metal alloys, including those essential to steel making. Iron and steel production account for 85–95% of the manganese market.

Occupational exposure occurs in mining, production of manganese metal and metal alloys, chemical production of manganese-based chemicals and six main manganese user sectors comprising: steel production, other metal smelting processes, fabrication (including welding), battery manufacture, agricultural products (production and use) and pigments, paints and glass making.

Workers can be exposed to dust and fumes of manganese-containing compounds in a range of particle sizes where the ratio of inhalable to respirable will vary within and between different industries (IEH, 2004). This has important implications for distribution and uptake within the respiratory tract.

In a study of exposure to manganese among welders using personal sampling devices, Harris and co-workers showed a close agreement between respirable manganese and total manganese fume. This study was done in an enclosed and restricted space (Harris *et al.*, 2005). Okamoto *et al*. have measured the variation in the ratio of respirable over inhalable particulates at several workplaces (not specifically involving Mn exposures). The following types of work were studied: grinding, power handling, founding, welding and miscellaneous work tasks. The regression coefficients between respirable and inhalable fractions varied from 0.46 to 0.86, the highest being found for welders (Okamoto *et al.*, 1998).

Manganese is an essential element; it is involved in bone formation and amino acid, cholesterol and carbohydrate metabolism; it is a component of several enzymes and activates others (IOM, 2002). For healthy adults, estimated acceptable or adequate dietary intakes range from 1–12.2 mg manganese/day (SCF, 1993; IOM, 2002; EVM, 2003).

2 Health significance

2.1 Toxicokinetics

Occupational exposure to manganese from welding, ore handling, production of manganese alloys and other uses are mainly through inhalation. In general, the extent of inhalation absorption is thought to be a function of particle size, because size determines the extent and location of particle deposition in the respiratory tract. While respirable manganese is readily taken up, larger particles are both directly taken up and some transported upward in the lung by mucociliary movement and finally swallowed and taken up in the intestine. Intestinal uptake is low, 3 to 5 %. The absorption of manganese from the gut is dependent on several factors, including the amount ingested, iron status and other dietary components. There is very tight biological regulation of the gastro-intestinal absorption of manganese which is not the case for inhalation exposure. Healthy adult humans not exposed to manganese by inhalation normally maintain stable tissue levels of manganese regardless of intake via homeostatic mechanisms; this homeostasis is maintained by regulation of absorption and excretion (IEH 2004 and ATSDR, 2000). In this context, 'normally' refers to the normal range of human variability and implies a non-pathological condition.

There is experimental evidence of olfactory uptake of manganese to the brain. The toxicological significance of this olfactory uptake to humans remains uncertain (IEH 2004; HC 2008)

In general the relationship between external exposure and biological parameters (blood or urine manganese concentration) is poor (IEH, 2004). However, when correlations were observed, they were generally better for the respirable than the inhalable fraction, pointing to the fact that the former is more extensively absorbed. As an example, in a study among manganese alloy production workers, Ellingsen *et al*. (2003) calculated a correlation coefficient equal to 0.7 between respirable and inhalable air manganese. These authors also determined the associations between manganese in biological fluids (blood and urine) and air manganese measured as inhalable and respirable. They found correlation coefficients (Pearson r) from 0.09 to 0.48; with the highest correlation coefficients between respirable manganese and manganese concentration in blood and urine.

Absorbed manganese is eliminated with a half-life of 10 to 30 days (Finley *et al* 2003). Manganese that is delivered to the brain is eliminated over time with reported half-life of 50 to 220 days (Newland 1987 and Takeda 1995 cited in HC 2008). It is important to recognise that accumulation and clearance of manganese from the brain might have important implications for neurofunctional effects which are reported in a range of occupational studies.

Toxicodynamic profile

Intentional or accidental ingestion of manganese as potassium permanganate suggests that 10 g can be fatal in humans (Huntley, 1984). In animals, the oral LD_{50} of inorganic

manganese compounds generally falls in the range 230 to 800 mg/kg (WHO, 1981). While no study on the acute lethality of manganese compounds via the inhalation route has been identified, significant, but non-lethal, pulmonary changes have been noted in mice exposed to manganese dioxide at 0.897 mg Mn/m^3.

Manganese exposure has been associated, in some studies, with adverse respiratory and cardiovascular effects; however, the neurological effects of manganese are considered to be the major concern for the establishment of occupational exposure limits (OELs see below). There is no strong evidence that manganese and its compounds, except permanganate, are irritants except at high exposure levels and, whilst limited, available data do not suggest that they have a strong sensitising potential. Data on carcinogenicity, mutagenicity and genotoxicity are inconclusive and inadequate to establish a definitive position on the carcinogenicity of manganese and its compounds. There is little evidence for reproductive or developmental toxicity.

Respiratory effects

Since the first report by Brezina in 1921, a number of studies have reported adverse respiratory effects following occupational manganese exposure. Effects reported include impairment of pulmonary function. These include decreases in forced vital capacity, FVC and forced expiratory volume in one second, FEV_1 among Asian miners (Boojar & Goodarzi, 2002), an increase in reported respiratory symptoms and impaired respiratory function (FVC, FEV_1) among chemical plant workers (Roels *et al.*, 1987), though with no dose-response relationship (Roels *et al.*, 1985), and increased respiratory morbidity among European ferroalloy plant workers and furnace workers (EPA, 1978; Hobbesland *et al.*, 1996; Hobbesland *et al.*, 1997a; Hobbesland *et al.*, 1997b). However, for a variety of reasons, some of these studies were unable to ascribe reliably the effects observed to manganese exposure. A study on the prevalence of lung symptoms among Belgian battery manufacturer workers (Roels *et al.*, 1992) failed to identify any pulmonary effects. In this study, exposed workers had been exposed for 5.3 years on average (range 0.2-17.7 years). The exposure range for total dust was 0.05-10.84 mg/m^3 (GM[1], 0.95 mg/m^3). The exposure range for respirable dust was 0.02-1.32 mg/m^3 (GM, 0.22 mg/m^3).

Experimental studies in animals suggest that inorganic manganese compounds are capable of causing pulmonary effects (inflammatory changes including fibrosis) when given by inhalation or the intratracheal route at sufficiently high dosages and/or for sufficiently long periods of time.

Cardiovascular and haematological effects

There is limited evidence that manganese may have an adverse effect on the human cardiovascular system (reduced systolic blood pressure) (e.g. Saric & Hrustic, 1975; EPA, 1978; Hobbesland *et al.*, 1997b) and may elicit haematological or biochemical changes (Roels *et al.*, 1987; Lucchini *et al.*, 1997). Some of these effects have also been found in animal studies.

Neurological effects

Although there is considerable evidence for clinical and subclinical neurotoxic effects of manganese, much less is known about the processes by which manganese passes into and moves within the central nervous system.

[1] GM: geometric mean; AM: arithmetic mean.

There is a substantial literature on the effects of manganese on the human nervous system. High exposures can result in severe neurotoxic signs and symptoms, some of which resemble those of idiopathic Parkinson's disease. This syndrome, which may also include psychiatric manifestations, has become known as 'manganism'. Manganese mainly induces damage to the globus pallidus (particularly the internal segment) with changes to the substantia nigra pars compacta and the absence of Lewy bodies. This contrasts with what is seen in Parkinson's disease, in which there is preferential degeneration of dopamine neurons in the substantia nigra pars compacta coupled with Lewy bodies and preservation of the pallidum. Overt manganism has been described in a number of early papers that reported studies on neurological signs and symptoms in workers with relatively high and long-term occupational exposures (Rodier 1955; Schuler *et al.*, 1957; Mena *et al.*, 1967; Chandra *et al.*, 1974). The clinical symptoms associated with manganism, such as movement disorders and neurological dysfunction, have generally been reported at exposure levels above 5 mg/m^3.

More recently, several studies on lower occupational exposures to manganese have reported less severe, subtle, non-clinical neurofunctional[2] effects. These subtle effects usually consist of deterioration in motor function and co-ordination and, as such, may constitute manganese-induced changes in the same area of the brain as manganism, that is the basal ganglia and, in particular, the globus pallidus.

Studies conducted up until 2004 on the identification of subtle neurofunctional effects and the levels at which they might occur have been summarised (IEH 2004). These studies have been evaluated for their methodological quality (assessed according to European Union recommended criteria for neurobehavioural studies; CEC, 1997) and the quality of exposure data. This latter document was prepared at the request of SCOEL for evaluation of neurotoxicity and its full title of "Criteria for the qualitative evaluation of human neurobehavioral studies of neurotoxicity" reflects its purpose as a guide for the qualitative evaluation and providing a reliable basis for using such studies for setting occupational exposure limits. Of the 28 studies considered, three key studies were identified. These were the cross-sectional studies of Roels *et al.* (1992), Gibbs *et al.* (1999) and Myers *et al.* (2002). Since this IEH 2004 evaluation, additional good quality studies have been published (Bast-Pettersen *et al.* 2004; Ellingsen *et al*. 2008; Myers *et al* 2003 a and b) and are included in the development of the IOELV proposals of this SCOEL Recommendation.

Longitudinal studies by Lucchini *et al.* (1999), Crump and Rousseau (1999) and Roels *et al*. (1999) provide information on the possible progression and reversibility of neurological effects and were discussed in the IEH 2004 review. These studies are included in this SCOEL Recommendation.

Roels et al. (1992) identified adverse effects on reaction time, tremor and hand–eye co-ordination in 92 workers exposed to manganese dioxide dust (with current average total and respirable fractions, 0.95 and 0.22 mg/m³ (GM), respectively, measured in each worker by personal sampling). Based on current exposure levels and the number of years in each job, the authors also estimated integrated exposure, which for respirable dust ranged from 0.040 to 4.433 and for total dust from 0.191 to 27.465 mg Mn/m^3 x years. The respective geometric means amounted to 0.793 and 3.505 mg Mn/m^3 x years. The exposed workers performed significantly less well than controls (n=110) for a number of neurofunctional parameters including visual reaction time, eye-hand coordination and hand steadiness. The prevalence of abnormal results in neurofunctional tests was related

[2] In this Document we use the word neurofunctional to cover a range of definitions used by investigators in their papers, to include neurobehavioural, neuropsychological and neurophysiological effects

to lifetime integrated exposure to manganese (total and respirable fractions). Using a logistic regression modelling, they reported that an increased risk of peripheral tremor (5% abnormal response increment) existed when the lifetime integrated exposure to total and respirable manganese dust exceeded **3.575** (p=0.029) and **0.730 mg/m³ x years** (p=0.054), respectively. These values can be regarded as LOAELs for this study.

In general support of the findings from Roels and colleagues, Mergler *et al.* (1994) also found adverse motor effects, but no effect on cognitive function, at low levels of exposure, among workers employed in ferromanganese and silicomanganese plants (average total and respirable fractions 0.225 and 0.035 mg/m³ (GM), measured by static sampling). However, there are concerns about the quality of reporting of the latter study and, as only results from static sampling were reported, it has not been possible to estimate reliably the equivalent levels that would have been found had personal sampling been used; therefore, less weight can be given to this study.

In contrast, the studies of Gibbs *et al.* (1999), among manganese metal (electrolytic) production workers (average total and respirable fractions 0.11 and 0.04 mg/m³ (GM), respectively, measured by personal sampling) also of good methodological quality, reported no neurofunctional effects. Some patterns in the data reported by Gibbs *et al.* (1999) were suggestive of an effect on psychomotor functions but were not statistically significant.

After performing their own reassessment of the data of Roels et al. (1992) and Gibbs et al. (1999), Clewell et al. (2003), based on a benchmark dose analysis, concluded that neurological effects induced by occupational exposure to manganese are best related to recent (not historical or cumulative) concentration of manganese in respirable (not total or inhalable) particulate.

As noted above, since the publication of the IEH report in 2004, a number of additional good quality neurofunctional studies on manganese-exposed workers have been published.

Myers and co-workers have published two papers dealing with nervous system effects among manganese smelters with measurements of inhalable (Myers *et al*., 2003b) and respirable dust (Young *et al*., 2005). The effects of manganese exposure on the nervous system have also been addressed in manganese mineworkers (Myers *et al*., 2003a).

In a cross-sectional study conducted in South African manganese mine workers (n=489) with contrasted levels of manganese exposure (administrative and services, engineering, processing and mining), Myers *et al*. (2003a) reported no evidence of neurofunctional manifestations caused by exposure. Manganese exposure was assessed with a job-exposure matrix constructed with governmental compliance data for total dust available over a period of 4 years in the mines included in the study. The percentage of manganese in the dust was estimated for each job from five pooled representative dust samples. Mean manganese total dust concentration was obtained by multiplying mean total dust concentration for each job with the mean manganese percentage content for that job. Additionally, a cumulative exposure index was calculated for each subject by multiplying the mean manganese dust concentration (total fraction) characteristic of each job by the number of years worked in that job, and summing these products over all jobs worked by each subject at the mines to the level of five previous jobs. Average intensity of exposure for each subject across all jobs exposed to manganese was then calculated by dividing the cumulative exposure index by total length of service in years at the mines. The average intensity of exposure was 0.210 mg/m³ manganese dust (arithmetic mean, total fraction) with a range from 0 to 0.990 mg/m³ and the duration of exposure varied between 1 and 41 years, with a mean of 10.8 years. The authors reported no influence of

any measure of exposure on a large battery of neurofunctional tests (maximum forward digit-span, maximum backward digit-span, digit-symbol score, mean reaction time). Effects of age and education level were, however, found, which was interpreted by the authors of the study as validating the reliability of their assessment. In view of the relatively indirect methodology to document individual exposure in this study, it might, however, be suspected that some degree of misclassification may have reduced the ability to detect a relationship with neurofunctional tests, if any.

In the manganese smelter study (Myers *et al*. (2003b)) examined 509 exposed workers and 67 controls; they used representative exposure estimates of inhalable manganese to characterise individual exposure. They reported a mean length of service of 18.2 years in smelters with average intensity of exposure of 0.82 mg/m^3 over these years and a mean cumulative exposure of 16 mg/m^3 x year. The authors concluded, "that this is essentially a negative study, providing only weak and unconvincing evidence for exposure effects in general, or for the notion of a continuum of effects." For the tremor data they stated that: "No exposure-response relationship was observed". A close analysis of this publication reveals, however, that several neurofunctional tests showed some differences between exposed workers and internal or external referents (digit span forward and backwards, digit symbol, endurance, finger tapping for dominant and non-dominant hand, Luria-Nebraska 1 and 2), and that for some endpoints (Luria-Nebraska item 1, digit symbol test, digit span, finger tapping) a dose-response relationship was established with cumulative exposure (mg/m³ x years). Furthermore, when the exposed workers were stratified into 5 exposure categories according to cumulative exposure, significantly altered parameters could be observed in the first quintile (Table 5). Overall, a cumulative exposure of **1.3 mg/m³ x years** (inhalable) can be taken as LOAEL in this study.

Table 5: Extracted from Myers et al. (2003b), Tables 3-5.

Cumulative exposure (mg/m³*years)	Digit span (forward, backward)	Digit symbol	Mean reaction time	Tapping dominant hand	Tapping non-dominant	LN1
Trend	+	+		+	+	+
>0-1.3	*			*		
1.3-5.4	***	*		***		
5.4-10.6	***	*	*	***	*	
10.6-22.4	***	**	***	*		*
>22.4	***	***		***	***	*

*, **, ***: significantly different from controls, p<0.05, 0.01 or 0.001, respectively

In an additional study of the same manganese smelters, they found that the median respirable manganese exposure (also estimated from a job-exposure matrix) was 0.058 mg/m^3 (range = 0–0.51) amongst the exposed (Young *et al*., 2005). The authors stated that their data did not provide empirical support for a respirable, as opposed to an inhalable, dust metric being more sensitive on the identification of manganese effects. A significant effect of Mn exposure (average exposure over the years of employment) was, however evident (see Tables 3 and 4 in the publication) for a number of neurofunctional

parameters (digit span, digit symbol, tapping and endurance), with a LOAEL in the range 0.010-0.040 mg/m³ (average respirable).

In a study among manganese alloy workers who had been exposed to manganese for 20.2 years on average (range from 2.1 to 41 years), Bast-Pettersen *et al.* (2004) analysed several potential nervous system effects of manganese exposure; among them tremor. Both the exposed and the reference groups consisted of 100 individuals. The concentration of manganese in air (inhalable fraction measured in each individual worker) ranged from 0.09 to 11.5 mg/m³ and the mean manganese exposure was 0.753 mg/m³ (AM) and 0.301 mg/m³ (GM). Respirable manganese exposure was 0.064 mg/m³ (AM) and 0.036 mg/m³ (GM) with a range from 0.003 to 0.356 mg/m³. The authors found statistically significant associations (using regression analysis) between tremor and exposure, tremor and age, and tremor and number of cigarettes per week. They showed two regression models for tremor (dependent variable) with years exposed and number of cigarettes/week as significant independent variables with a R^2 equal to 0.16. There was a statistically significant difference in tremor between the reference and exposed groups analysed with the Kløve-Matthews' Static Steadiness test. The mean arithmetic value for duration of contacts and number of contacts in the exposed group was 94 (5.1 sec) and the reference group 59 (5.1 sec). Measurements of duration of contacts showed a dose-response relationship when dividing the total population in reference (unexposed), and exposed subgroups with mean duration of exposure at 11.5 years, 19.3 years and 29.1 years. For several of the neurofunctional functions tested, there was no significant difference between exposed and referents. This study indicates that duration of exposure is a significant determinant of manganese toxicity and suggests a LOAEL for non-clinical hand tremor around the mean manganese exposure in the exposed group (**0.301 inhalable and 0.036 mg/m³ respirable** (GM)).

In a neurofunctional study of current and former welders exposed to manganese, Ellingsen *et al*. (2008) reported associations between the digit symbol and finger tapping test scores and blood-manganese and air-manganese. The current welders and the reference group consisted both of 96 individuals. The current welders were aged between 20 - 65 years (36.3 AM). Manganese exposure was measured with filter cassettes that collected total dust for each worker. The cassettes were placed in the breathing zone underneath the welding helmet. Current welders had an exposure of 0.238 mg/m³ (AM) and 0.121 mg/m³ (GM) with a range from 0.007 to 2.311 mg/m³. Static steadiness was measured as number (and duration) of contacts. Current welders performed significantly better than referents with AM of 142 (6.7 sec) with a range of 5 - 656 (0.4s - 37.7s) compared to the referents: 184 (11.2 sec); 5 - 603 and (0.3 - 32.2) The authors explained this result by work practice; a steady hand being important in welding and they refer to similar findings in a neurobehavioral study in aluminium welders (Bast-Pettersen et al., 2000). Finger tapping data stratified in low, medium and high exposure (0.031, 0.137 and 0.423 mg/m³ GM) showed, however, a dose-response with significantly worse performances in the high exposure group (**LOAEL 0.423 mg/m³ for total dust and 0.338 mg/m³ for respirable dust** assuming a 80% Respirable/Total dust ratio) and non-significant effects in the medium exposed group which can be defined as a NOAEL (0.137 mg/m³ for total dust or 0.110 mg/m³ for respirable dust; assuming a 80% Respirable/Total ratio).

Included in this neurobehavioral study were also 27 patients with the diagnosis of manganism, officially recognized 5.8 years prior to this study as an occupational disease in the Russian insurance system. All the patients in this study were former welders and a comparison was made between the patients, 42 of the current welders and 42 referents from the original study groups. All participants in these groups were aged over 41 year. The patients who had worked as welders for 23.1 years had a significantly higher tremor than the referents and current welders. The Static steadiness data, arithmetic mean of number

and duration of contacts of the patients, in current welders and referents was 360 (20.5 sec), 156 (7.2 sec) 212 (13.3 sec) respectively.These results point to the probable irreversibility of some of the neurofunctional damage induced by long-term manganese exposure.

In relation to the suggestion of irreversibility from this latter study, some longitudinal information is available to assess the progression and/or reversibility of manganese-induced neurofunctional changes from other studies. Lucchini *et al.* (1999) confirmed motor function changes identified in a group of ferroalloy workers examined in an earlier study (Lucchini *et al.*, 1995) but found no evidence of progressive deterioration in these workers, whose exposure to manganese had been reduced in the interim period. Similarly Crump and Rousseau (1999) followed up chemical production workers, originally studied by Roels *et al.* (1987), and found little or no evidence of progression of neurobehavioural effects. Alongside this, Roels *et al.* (1999) found only limited evidence for the reversibility of adverse effects identified in battery workers who were re-tested following an 8-year period during which exposure had been reduced. Reversibility of neurofunctional changes was only observed in the cohort of workers who had been exposed to an average level of 0.400 mg Mn/m³ (total dust) and whose exposure had dropped to 0.130 mg Mn/m³ by the end of the study.

From these above studies, it can be concluded that there is likely to be some reversibility of the damage in neurofunctional associated with manganese exposure following cessation or reduction of exposure but the available data do not allow this reversibility to be quantified.

Most recently, Health Canada (HC) 2008 has produced an environmental risk assessment for inhaled respirable manganese based upon the Lucchini *et al* (1999) study in Italian ferroalloy workers, selected as the key study. They have produced a quantitative risk assessment using a benchmark concentration analysis approach based on two exposure metrics. One of these is based on a life-time exposure to respirable manganese and the second, on an average exposure to respirable manganese over the last five years prior to testing. As yet, the exposure data for these analyses has not been published, but HC 2008 has used it to produce a reference concentration of 0.05 µg/m³ for manganese (environmental exposure). This value is derived from a **benchmark dose calculation of 0.02 mg/m³** (5% increased risk based on 5 last years average exposure levels) using the performance in the Luria-Nebraska tests as the most sensitive endpoint in the group of Italian workers (HC 2008).

Considering the variation in methodologies, exposure patterns, particle size distribution and types of manganese compounds, as well as smoking habits (this latter has been shown to have an effect upon tremor, Bast-Pettersen et al 2004), it is not surprising that there are differences and apparent inconsistencies across all the above described studies. However, it is important to look for consistent patterns of effects (such as fine motor control) in these studies and accept the fact that not all were conducted with comparable methodologies and involved varying occupational settings and populations with different ethnic and cultural backgrounds which may also in part contribute to these variations. For a thorough understanding of the heterogeneous data for health-exposure associations, the readers are referred to the IEH Criteria Document (2004).

More recently, a meta-analysis of 13 epidemiological studies conducted between 1987 and 2008, including a total of more than 900 exposed workers (0.05-1.600 mg Mn/m³, inhalable) and 800 controls concluded that an adverse impact of Mn exposure exists, mainly on motor, and to a lesser extent, cognitive performances (Meyer-Baron et al. 2009).

Most work in experimental animals has focused on identifying underlying mechanisms of toxicity; however, because of inter-species differences these studies are of limited value in understanding mechanisms in humans. Many studies on rodents indicate that they do not handle manganese in the same way as humans or primates, and rodents appear to be more sensitive to manganese than humans; direct comparison may not, therefore, be relevant. In particular, while rodents are able to absorb manganese via the olfactory bulb with subsequent direct accumulation in the brain, this route has not been established in humans. In humans and primates, manganese appears to accumulate in the basal ganglia (in particular, the globus pallidus), while in rodents manganese is more widely distributed throughout the brain (Nishiyama *et al.*, 1977; Ulrich *et al.*, 1979a; Ulrich *et al.*, 1979b). Few studies in experimental animals provide information on dose-response, and none is of assistance in setting a no-observed-adverse-effect-level (NOAEL). The best estimate for an oral lowest-observed-adverse-effect-level (LOAEL) in rodents lies between 10 and 40 mg/kg/day, with alterations in brain biogenic amine levels and motor activity being the key endpoints (e.g. Subhash & Padmashree, 1991). Neurobehavioural and neurochemical effects have been seen in rats after inhalation exposure to manganese, with a LOAEL of 3.75 mg/m^3 (St-Pierre *et al.*, 2001), while studies in monkeys have given apparently conflicting results (Bird *et al.*, 1984).

Although evidence is limited, the carcinogenicity, mutagenicity, genotoxicity, and reproductive toxicity profiles for manganese and its compounds do not suggest that these aspects are key to an evaluation of occupational exposure standards (IEH 2004).

Summary of health effects

The review of the vast literature (IEH 2004) on the toxic effects of manganese exposure presented and discussed in this SCOEL Summary document highlights the fact that a range of different adverse health effects may occur following occupational exposure to manganese.

Non-neurological effects

Pulmonary effects associated with manganese exposure do not appear to occur at levels below those at which identifiable neurological changes can be detected (Roels *et al.*, 1992). Adverse effects on the cardiovascular system (reduction in systolic blood pressure) appear to occur at levels similar to or above those at which pulmonary changes occur. Neither of these effects, therefore, is considered to be key to the establishment of occupational exposure standards, and it appears that neither respiratory nor cardiovascular toxicity would be expected at inhalable exposures of 1 mg/m^3 or less.

Neurological effects

Although manganism has long been recognised as being associated with high occupational manganese exposures, recent attention has focused on more subtle neurofunctional effects that may occur at lower levels of exposure. A recent review of the evidence (IEH 2004), supported by additional studies published since this review, has led to the conclusion that, in humans, the critical effects associated with contemporary (low) occupational exposure to manganese are neurological. These subtle neurological effects, that is, principally small sub-clinical neuromotor effects, are considered to be of sufficient concern to warrant the establishment of an appropriate occupational exposure standard. A limited number of longitudinal investigations on these more subtle effects indicate a stability (lack of progression) of adverse effects when exposure is reduced, but also indicate that such effects, once established, may not be reversible. Furthermore, most of the neurofunctional effects observed reflect changes in neuromotor function, as is the

case with overt manganism. There are a sufficient number of well-conducted studies on workers exposed to known or reasonability well-estimated amounts of manganese to use human data for the derivation of a health-based Indicative Occupational Exposure Limit Value (IOELV).

Recommendations for scientifically-based occupational exposure limits

It is important that any metric(s) used for limit setting should be that most closely associated with the critical endpoint. The most sensitive endpoint for manganese exposure is neurological (i.e. systemic rather than at the principal point of entry, the lungs) and, for manganese, the respirable fraction is considered to be the best indicator of systemic availability. However, it is also appropriate to consider that every inhaled fraction reaching the respiratory tract contributes to workers' exposure, being via rapid and complete absorption in the alveoli, dissolution in the airway mucus, some olfactory uptake in the upper airways or limited gastro-intestinal uptake after mucociliary clearance and deglutition. A large proportion of the inhaled fraction will, however, ultimately enter the gastrointestinal tract, yet gastrointestinal absorption is fairly low, even for soluble forms of manganese (~5%), and there is little evidence for manganese toxicity following dietary exposure. Uptake of dietary manganese is controlled by dose-dependent intestinal absorption, biliary excretion and intestinal elimination (Anderson *et al*, 1999, cited in IEH 2004). Adult humans normally maintain stable tissue levels of manganese regardless of intake; this homeostasis is maintained by regulation of absorption and excretion (ATSDR 2000). It is, therefore, recommended that the most biologically appropriate measure of exposure to airborne manganese for evaluating health effects and setting an occupational exposure standard is the **respirable aerosol** rather than total or inhalable aerosol. This approach is supported by data comparing the respirable and inhalable aerosol fractions in fields studies (e.g. Ellingsen *et al*. 2003)

Manganese dust may, however, vary in particle size depending on the industry sector and the process involved. The complex relationship and ratios between total, inhalable and respirable manganese particulates has been described and discussed in depth (IEH, 2004) in relation to most occupational scenarios that are likely to be encountered. The respirable fraction (hence the respirable to inhalable [or total] ratio) may, therefore, vary widely and it is recognised that this has practical implications for setting standards. In processes where the respirable to inhalable (or total) ratio is low, gastrointestinal absorption may not be, after all, insignificant, which may be the case in some processes. An **inhalable limit** is therefore also recommended. In support of this two-metric approach, it is useful to consider that Lauwerys *et al*. (1992) stated: "In industry, evaluation of individual exposure to manganese is thus best carried out by monitoring its concentration in total and respirable dust in the breathing zone of the workers."

The relative importance of cumulative versus current or peak exposure in determining risks is not exactly known. However, on the evidence available, including biological plausibility, **cumulative exposure** appears the best way to represent the time-relatedness of manganese exposure and effect for the purposes of setting an IOELV. It is also relevant as it may be that, as shown in some studies, not all the reported neurofunctional effects seen in longitudinal investigations of workers effects are reversible.

Because of the heterogeneity of the data (different types of industry, different manganese compounds and particle sizes, different study designs and different neurofunctional measurements), and the inherent limitations of every individual study, **it is not possible to**

identify one single critical study that would be the best basis for setting the IOELVs. Some studies identified a LOAEL, other a NOAEL. Some studies relied on the respirable fraction; other on the inhalable or "total" (thoracic) fraction. A global approach using the most methodologically-sound studies, as used in the IEH Criteria document (2004) and a number of additional good quality studies published since this review was therefore considered to be the most robust and reliable approach. The studies by Roels *et al*. (1992), Gibbs *et al.* (1999) Myers *et al.* 2003b, Young *et al*. 2005, Bast-Pettersen *et al.* (2004) and Ellingsen *et al.* (2008) as well as Lucchini *et al.* 1999 in HC (2008) which showed adverse neurological effects and identified a point-of-departure (POD) in the dose-effect/response relationship may offer a basis for recommending an IOELV.

Thus, a reasonable **respirable IOELV** of **0.05 mg/m³** can be recommended, and a reasonable **inhalable IOELV** of **0.2 mg/m³** is also recommended. While recommending these values, SCOEL recognises that the overall systemic absorption of coarser particles (> respirable) is probably substantially lower than for the respirable fraction. Thus, SCOEL recommends both a respirable and an inhalable IOELV which would need to be observed conjointly.

It is recommended that workplaces should, as a default procedure, measure both respirable and inhalable manganese to ensure compliance with both limits. This will protect workers exposed to respirable manganese, such as welders, and also workers exposed to inhalable manganese in workplaces with low fractions of respirable manganese. In each specific working circumstance, professional judgement should however, be applied to select the most appropriate fraction to be measured.

When considering all these above studies and arriving at these proposed IOELVs, a number of issues need, however, to be taken into account:

- The changes reported in the above described studies are subtle early neurofunctional effects which are non-clinical in nature and are only detected at a statistical level between groups of workers.

- It should also be considered that some of these subtle neurofunctional effects of manganese on the CNS are irreversible although the degree of reversibility has not been defined.

- Most of the available studies used in this evaluation have a cross- sectional design, and thus it is highly likely that any recorded neurofunctional effects may be the result of previously higher exposure levels not reflected in current measurements [**left shift bias in the evaluation of the dose-effect/response relationships**] There is indeed evidence from a longitudinal study in exposed workers that, while exposure levels decreased over the time, neurofunctional deficits persisted for some functional endpoints (Roels *et al*, 1999).

- Some of the above studies (Roels *et al*. 1992; HC 2008) used **non-threshold functions** to model dose-response relationships at low exposure levels, which may contribute to **overestimate the risk,** if such a threshold exists.

- Finally, in many of the studies discussed, **arithmetic means**, **geometric means** or both have been used to characterise "average" worker exposures. In this current SCOEL recommendation we have presented geometric means to characterise the PODs. This is considered to be the **most conservative** approach for setting an OEL

however, Crump (1998) recommends that generally, the arithmetic mean is more representative of true average exposures. In practice, GMs are approximately half the numerical values of the AM.

SCOEL considered that all these above five factors would provide a further degree of precaution to the protection against any neurofunctional change provided by the recommended IOELVs

In addition to these above conclusions and deliberations, SCOEL additionally considered a number of worst-case scenarios from a number of the above key studies in order to satisfy themselves that these IOELV recommendations were sufficiently protective. Among these studies, three identified a POD based on cumulative exposure:

- The study by Roels *et al*. (1992) suggests a LOAEL of 0.730 (respirable) or 3.575 (total) mg/m³ x years, predicting that workers exposed during 20 years to **0.036 (respirable)** or 0.178 mg Mn/m³ (total) would be at risk of presenting with early neurofunctional changes caused by manganese (5% increased risk of abnormal neurofunctional performance).

- The study by Myers *et al*. (2003b) suggests a LOAEL of 0.871 (respirable) or 1.3 (inhalable) mg/m³ x years, predicting that workers exposed during 20 years to or **0.065 (inhalable)** mg Mn/m³ would be at risk of presenting with early neurofunctional changes caused by manganese. The LOAEL expressed as the **respirable** fraction is between **0.010 and 0.040** in this cohort (Young *et al*. 2005)

- The HC (2008) evaluation suggests that workers exposed during the last 5 years to an average concentration of **0.050 mg Mn/m³ (respirable)** would present a 5% increased of reduced neurofunctional performance (LOAEL).

Two other studies identified POD based on current exposure levels:

- The study by Bast-Pettersen *et al*. (2004) suggests that workers exposed to **0.036 (respirable)** or **0.301 (inhalable)** mg Mn/m³ would be at risk of presenting with early neurofunctional changed caused by manganese (LOAEL).

- The study by Ellingsen *et al*. (2008) suggests that workers exposed to **0.338 (respirable)** or **0.423 (t)** mg Mn/m³ would be at risk of presenting with early neurofunctional changes caused by manganese (LOAEL).

- However, Gibbs *et al*. (1999) did not detect an effect of occupational manganese exposure on neurofunctional performances (NOAEL) in workers exposed on average to **0.040 mg Mn/m³ (respirable)**.

The results from this approach, based on worst-case scenarios, gave results which were remarkably close to the two SCOEL IOELV recommendations and thus confirmed their appropriateness as health-based IOELVs.

,

A short-term exposure limit (STEL) is not required.

Biological Monitoring of manganese:

Owing to poor correlations with airborne levels and the high individual variability of blood and urine levels in those studies used in the development of the Criteria Document (IEH,

2004) on which this SCOEL/SUM is mainly based , it is not possible to confidently set health-based biological standards for manganese in blood and urine. Most investigators have concluded that there is no good relationship between manganese in blood or urine and the severity of health effects, probably because individual susceptibility plays an important role. Lucchini *et al*. (1995), however, found significant correlations between blood and urine Mn levels and the performance of several neurofunctional tests in workers removed from exposure. Their data do not suggest a critical effect level. Therefore, the possibilities for monitoring exposure to manganese by biological methods remain limited. The measurement of manganese in urine and blood can probably be recommended to The measurement of manganese in urine and blood can probably be recommended to confirm increased exposure to manganese at the group level (Lauwerys and Hoet, 2001). This would mean a significant increase of the mean of the concentration of manganese in blood and urine in a group of cadmium-exposed workers compared to concentrations in a matched (age, gender, etc) group of non-cadmium-exposed workers. In Germany, a Biologischer Arbeitsstoff-Referenzwert (BAR) value of 15 µg/l blood has been established by the MAK Commission. This value represents manganese concentrations in the general population (95th. percentile) not occupationally-exposed to manganese, but in the working age (Drexler and Hartwig, 2011).

References

ATSDR Agency for Toxic Substances and Disease Registry September 2000 Toxicological Profile for Manganese, available at http://www.atsdr.cdc.gov/toxprofiles/tp151.html

Bast-Pettersen R, Ellingsen DG, Hetland SM, Thomassen Y (2004) Neuropsychological function in manganese alloy plant workers. Int Arch Occup Environ Health 77: 277-287

Bast-Pettersen R, Skaug V, Ellingsen D, Thomassen Y (2000) Neurobehavioral performance in aluminium welders. Am J Ind Med 37: 184-192

Bird ED, Anton AH & Bullock B (1984) The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey. Neurotoxicology, 5, 59-66

Boojar MMA & Goodarzi F (2002) A longitudinal follow-up of pulmonary function and respiratory symptoms in workers exposed to manganese. J Occup Environ Med, 44, 282-290

Brezina E (1921) Internationale Übersicht über GewerbeKrankheiten, Berlin, Germany, Springer

CEC (1997) Occupational Exposure Limits. Criteria for the Qualitative Evaluation of Human Neurobehavioural Studies of Neurotoxicity (EUR 17390 EN), Brussels, Belgium, Commission of the European Communities

Chandra SV, Seth PK & Mankeshwar JK (1974) Manganese poisoning: Clinical and biochemical observations. Environ Res, 7, 374-380

Clewell HJ, Lawrence GA, Calne DB, Crump KS (2003) Determination of an occupational exposure guideline for manganese using the benchmark method. Risk Anal 23: 1031-1046

Crump KS (1998) On summarizing group exposures in risk assessment: is an arithmetic mean or a geometric mean more appropriate? Risk Anal 18: 293-297

Crump KS & Rousseau P (1999) Results from eleven years of neurological health surveillance at a manganese oxide and salt producing plant. Neurotoxicology, 20, 273-286

Drexler H., Hartwig A. (Hrsg.) Mangan (Addendum) Biologische Arbeitsstoff-Toleranz-Werte (BAT-Werte), Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA), Biologische Leitwerte (BLW) und Biologische Arbeitsstoff-Referenzwerte (BAR). 18. Ergänzungslieferung. Wiley-VCH, Weinheim.

EPA (1978) Biological Effects of Manganese (EPA-600/1-78-001), USA, US Environmental Protection Agency, Office of Research and Development

EVM (2003) Safe Upper Levels for Vitamins and Minerals (Report of the Expert Group on Vitamins and Minerals), London, UK, Food Standards Agency

Ellingsen DG, Hetland SM, Thomassen Y (2003) Manganese air exposure assessment and biological monitoring in the manganese alloy production industry. J Environ Monit 5: 84-90

Ellingsen DG, Konstantinov R, Bast-Pettersen R, Merkurjeva L, Chashchin M, Thomassen Y, Chashchin V (2008) A neurobehavioral study of current and former welders exposed to manganese. Neurotoxicology 29: 48-59

Finley JW, Penland JG, Pettit RE and Davis CD (2003) Dietary Manganese Intake and Type of Lipid Do Not Affect Clinical or Neuropsychological Measures in Healthy Young Women. The American Society for Nutritional Sciences J. Nutr. 133:2849-2856

Gibbs JP, Crump KS, Houck DP, Warren PA & Mosley WS (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

Harris MK, Ewing WM, Longo W, DePasquale C, Mount MD, Hatfield R, Stapleton R (2005) Manganese exposures during shielded metal arc welding (SMAW) in an enclosed space. J Occup Environ Hyg 2: 375-382

HC 2008 Human Health Risk Assessment for Inhaled Manganese Draft Water, Air & Climate Change Bureau Health Canada, March, 2008 http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/air/out-xt/_consult/draft_ebauche/manganese_e.pdf

Hobbesland Å, Kjuus H & Thelle DS (1996) A study of mortality among 14 730 male workers in 12 Norwegian ferroalloy plants: Cohort characteristics and the main causes of death. Occup Environ Med, 53, 540-546

Hobbesland Å, Kjuus H & Thelle DS (1997a) Mortality from cardiovascular diseases and sudden death in ferroalloy plants. Scand J Work Environ Health, 23, 334-341

Hobbesland Å, Kjuus H & Thelle DS (1997b) Mortality from nonmalignant respiratory diseases among male workers in Norwegian ferroalloy plants. Scand J Work Environ Health, 23, 342-350

Huntley AC (1984) Oral ingestion of potassium permanganate or aluminium acetate in two patients. Arch Dermatol, 120, 1363-1365

IEH (2004) Occupational Exposure Limits: Criteria Document for Manganese and Inorganic Manganese Compounds (Web Report W17), Leicester, UK, MRC Institute for Environment and Health

IOM (2002) Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc, Washington DC, USA, National Academy Press, available [December 2002] at http://books.nap.edu/books/0309072794/html/394.html

Lauwerys and Hoet (2001) Industrial chemical exposure – Guidelines for biological monitoring. Third edition – Lewis publishers, Boca Raton, USA.

Lauwerys RR, Bernard A, Roels H, Buchet JP, Cardenas A, Gennart JP (1992) Health risk assessment of long term exposure to chemicals: application to cadmium and manganese. Arch Toxicol Suppl 15: 97-102

Lucchini R, Apostoli P, Perrone C, Placidi D, Albini E, Migliorati P, Mergler D, Sassine M-P, Palmi S & Alessio L (1999) Long term exposure to "low levels" of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology, 20, 287-298

Lucchini R, Bergamaschi E, Smargiassi A, Festa D & Apostoli P (1997) Motor function, olfactory threshold, and hematological indices in manganese-exposed ferroalloy workers. Environ Res, 73, 175-180

Lucchini R, Selis L, Folli D, Apostoli P, Mutti A, Vanoni O, Iregren A & Alessio L (1995) Neurobehavioral effects of manganese in workers from a ferroalloy plant after temporary cessation of exposure. Scand J Work Environ Health, 21, 143-149

Mena I, Marin O, Fuenzalida S & Cotzias GC (1967) Chronic manganese poisoning: Clinical picture and manganese turnover. Neurology, 17, 128-136

Mergler D, Huel G, Bowler R, Iregren A, Bélanger S, Baldwin M, Tardif R, Smargiassi A & Martin L (1994) Nervous system dysfunction among workers with long-term exposure to manganese. Environ Res, 64, 151-180

Meyer-Baron M, Knapp G, Schapper M, and van Thriel C (2009) Performance alterations associated with occupational exposure to manganese – A meta-analysis. doi:10.1016/j.neuro.2009.05.001

Myers JE, teWaterNaude J, Fourie M, Zogoe HB, Naik I, Theodorou P, Tassel H, Daya A, Thompson ML (2003a) Nervous system effects of occupational manganese exposure on South African manganese mineworkers. Neurotoxicology 24: 649-656

Myers JE, Thompson ML, Ramushu S, Young T, Jeebhay MF, London L, Esswein E, Renton K, Spies A, Boulle A, Naik I, Iregren A, Rees DJ (2003b) The nervous system effects o occupational exposure on workers in a South African manganese smelter. Neurotoxicology 24: 885-894

Nishiyama K, Suzuki Y, Fujii N, Yano H, Ohnishi K & Miyai T (1977) Biochemical changes and manganese distribution in monkeys exposed to manganese dioxide dust. Tokush J Exp Med, 24, 137-145

Okamoto S, Nakagoshi S, Ukai H, Takada S, Inui S, Higashikawa K, Ikeda M (1998) Variation in the ratio of respirable particulates over inhalable particulates by type of dust workplace. Int Arch Occup Environ Health 71: 111-116

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

Roels HA, Eslava MIO, Ceulemans E, Robert A & Lison D (1999) Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. Neurotoxicology, 20, 255-271

Roels HA, Ghyselen P, Buchet JP, Ceulemans E & Lauwerys RR (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, Lauwerys R, Buchet J-P, Genet P, Sarhan MJ, Hanotiau I, de Fays M, Bernard A & Stanescu D (1987) Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system and some biological indices. Am J Ind Med, 11, 307-327

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, 210-206

Saric M & Hrustic O (1975) Exposure to airborne manganese and arterial blood pressure. Environ Res, 10, 314-318

SCF (1993) Reports of the Scientific Committee for Food (Thirty-first Series), Luxembourg, Office for Official Publications of the European Communities

Schuler P, Oyanguren H, Maturana V, Valenzuela A, Cruz E, Plaza V, Schmidt E & Haddad R (1957) Manganese poisoning: Environmental and medical study at a Chilean mine. Ind Med Surg, 26, 167-173

St-Pierre A, Normandin L, Carrier G, Kennedy G, Butterworth R & Zayed J (2001) Bioaccumulation and locomotor effect of manganese dust in rats. Inhal Toxicol, 13, 623-632

Subhash MN & Padmashree TS (1991) Effect of manganese on biogenic amine metabolism in regions of the rat brain. Food Chem Toxicol, 29, 579-582

Ulrich CE, Rinehart W & Brandt M (1979a) Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. III - Pulmonary function, electromyograms, limb tremor and tissue manganese data. Am Ind Hyg Assoc J, 40, 349-353

Ulrich CE, Rinehart W & Busey W (1979b) Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol - I. Introduction, experimental design, and aerosol generation methods. Am Ind Hyg Assoc J, 40, 238-244

Young T, Myers JE, Thompson ML (2005) The nervous system effects of occupational exposure to manganese—measured as respirable dust—in a South African manganese smelter. Neurotoxicology 26: 993-1000

WHO (1981) Manganese (International Programme on Chemical Safety, Environmental Health Criteria, 17), Geneva, Switzerland, World Health Organization