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Review Article

Setting Evidence-Based Occupational Exposure Limits for Manganese

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Abstract

In 2004, a review by the Institute of Environment and Health (IEH) made recommendations on occupational exposure limits (OELs) for manganese and its inorganic compounds for inhalable and respirable fractions respectively. These OELs were based on a detailed comprehensive evaluation of all the scientific data available at that time. Since then, more published studies have become available and a number of occupational standard-setting committees (EU SCOEL, US ACGIH-TLV, and Germany MAK) have proposed OEL's for manganese and its inorganic compounds that are somewhat lower that those proposed in the 2004 review.

Based on current understanding, the key toxicological and human health issues that are likely to influence a health-based recommendation relate to: neurotoxicology; reproductive and developmental toxicology; and mutagenicity/carcinogenicity. Of these, it is generally considered that neurotoxicity presents the most sensitive endpoint. As such, many of the studies that have been reported since the IEH review have sought to use those neurofunctional tests that appear to be particularly sensitive at identifying the subtle neurological changes thought to associate with manganese toxicity. These recent studies have, however, continued to be limited to a significant extent by reliance on cross-sectional designs and also by use of unreliable exposure estimation methods. Consequently the strength of the potential association between manganese exposure and these subtle subclinical cognitive or neuromotor changes is still poorly characterised and the relevance of these minor differences in terms of either their clinical or quality of life consequences remains unknown.

Based upon the overall evidence, it is concluded that the 8-hr time weighted averages (TWA) for respirable (0.05 mg/m^3 as Mn) and inhalable (0.2 mg/m^3 as Mn) fractions as recommended by the SCOEL in 2011 are the most methodologically-sound, as they are based on the best available studies, most suited to the development of health-based OELs for both respirable and inhalable fractions. The dose-response characterisation informed by the examined studies used can be considered to establish a true human NOAEL for all the neurofunctional endpoints examined within the selected studies.

Keywords

manganese; occupational exposure limit; neurotoxic; respirable; inhalable

1 Introduction

The purpose of this paper is to review and describe the development of contemporary recommended or set occupational exposure limits (OEL) for manganese and its inorganic compounds by a number of authorative OEL-setting bodies in Europe and the USA. The process ,as will be shown, is complex as the most informative studies are those using groups of exposed workers who have been exposed to a range of different manganese compounds of differing solubility and particle size and measured by different sampling metrics (respirable, inhalable and total). Unfortunately, airborne exposure of workers cannot reliably be validated by biological monitoring as, due to the homeostatic control of manganese by the liver, there is no clear correlation between long-term exposure to manganese and its inorganic compounds and the biological monitoring of manganese in the urine or blood (Zheng et al. 2011; Laohaudomchok et al., 2011; Gil et al., 2011). To add to this complexity, none of the worker studies of the subtle neurofunctional (cognitive and motor) effects reported have used the same battery of tests with a standardised protocol. This makes comparison of the studies somewhat problematical.

2 Overview of OEL setting

Occupational Exposure Limits (OELs) have now been a feature of the industrialised world for many decades. The objective of OELs is to set limits for exposure via the airborne route such that exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time (as far as can be predicted from the contemporary state of knowledge). OELs may be established using human and/or animal data and are intended to be protective under realistic workplace exposure conditions (e.g. by mandating controls on the maximum exposure during a working day or on peak short-term exposures) (EC, 2013). The EU Scientific Committee on Occupational exposure Limits (SCOEL) advises that OELs may principally be used ‘to provide standards or criteria against which measured exposure levels in existing workplaces may be compared in order to ensure that, as far as the current state of knowledge permits, control is adequate to protect health’. However, OELs can also be used for designing new plants and processes to ensure that they ‘are engineered in such a way that exposures can be controlled at levels which will not damage health’ (EC, 2013). In general OELs are used by risk managers to ensure that workers are not exposed to substances above the OEL whether it is an 8-hr TWA or 15min STEL. This often results in exposures well under the OEL (guideline or statutory).

Various but similar approaches exist for setting OELs and, depending on the particular socioeconomic, legislative and political environment, different regulatory bodies (e.g. SCOEL[1] in the EU, MAK[2] in Germany and the American Conference of Governmental Hygienists[3] (ACGIH) in the US) may reach somewhat differing conclusions as to what constitutes the appropriate OEL for a substance.

2.1 Health based vs. risk based OELs

[1] http://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en
[2] http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/
[3] http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations/overview

Health based OELs: these are established where the available scientific data base leads to the conclusion that it is possible to identify a clear threshold dose/exposure level below which exposure is not expected to lead to adverse effects (EC, 2013). These OELs do not take into account socioeconomic or achievability factors.

Risk-based OELs: these are established when it is not possible on present knowledge to define a threshold of activity (e.g. genotoxicity, carcinogenicity and respiratory sensitisation) it must be assumed that any level of exposure, however small, might carry some finite risk (EC, 2013). In the EU it is the responsibility of the Commission to set 'risk-based' OELs, which requires consultation with interested parties (EC, 2013). Alternatively, a health-based limit could be set but socioeconomic and/or achievability are taken into account. In practical terms, this means that the available data would allow the establishment of a health-based limit but, the stakeholders (government, trade unions and industry) may negotiate to establish an OEL above the concentrations(s) of the health-based limit due to socioeconomic or practical reasons.

2.1.1 General procedure for setting health-based OELs

For chemicals where a threshold of adverse health effect (immediate or delayed) has been identified from good quality human and experimental studies, OELs are established by application of an uncertainty factor (Dankovic et al., 2015) to a point of departure (e.g. N(O)AEL, L(O)AEL or BMD) for the most sensitive adverse health effect in this case neurotoxicity. Expert judgement is usually needed by these OEL-setting committees on a case-by-case basis to determine an appropriate uncertainty factor. OELs are established in relation to a reference period of **8 hours**, for a **40-hour working** week and for a **working lifetime** (8-hour TWA[4] OEL) and expressed as ppm or mg/m^3.

For some threshold chemicals, compliance with an 8-hour TWA does not adequately control the adverse health effects, and short-term exposure limits (15 min. STELs) are set. This is likely to arise for substances for which a critical effect is observed following a brief exposure (e.g. CNS depression) and where the 8-hour TWA OEL is established at a level not very much lower than exposures at which there might be a risk of short-term effects occurring.

In addition, for chemicals where biological monitoring data is available, biological limit values (BLVs) can be set. These define levels of substances in humans, their metabolite, or indicator of effect e.g. in blood, urine or breath in workers exposed to the chemical in question at the level of the OEL. Although biomonitoring provides information about total exposure from all routes (inhalation, ingestion and dermal), in an occupational setting inhalation is most likely to be the predominant route of exposure, particularly when considering Mn industries. . BLVs do not indicate a sharp distinction between hazardous and non-hazardous exposures. For many substances, the data are too limited to support a biological monitoring method, or a metabolite or indicator cannot be defined.

[4] TWA – time weighted average for the exposure to a chemical can be used when both the chemical concentration and time for exposure varies. For gases the units are in parts per million (ppm) and for particulates such as dust, smoke and mist, units are in milligrams per cubic meter (mg/m^3).

Where data is inadequate to set a BLV, a biological guidance value (BGV) can be established. This refers to the upper concentration of the substance (or a metabolite) in biological medium corresponding to a certain percentile (generally 90th or 95th percentile) in a defined reference population. These values can be helpful in identifying where risk management measures may be introduced to reduce exposure.

2.1.2 OEL procedure for non-threshold chemicals

There is growing recognition that carcinogenic risk extrapolation to low doses (and standard setting) must consider the mode of action of a given chemical. To date there is a general agreement to distinguish between genotoxic and non-genotoxic chemicals, but further differentiation based on mode of action also seems appropriate (Bolt & Huici-Montagud, 2008). This means that a threshold approach may be applied for some carcinogens. In the EU, SCOEL distinguishes 4 types of carcinogen on mechanistic grounds, namely:

Group A: Non-threshold genotoxic carcinogens - for low-dose risk assessment linear non-threshold (LNT) modelling is applied;

Group B: Genotoxic carcinogens – where a threshold cannot be sufficiently established, LNT modelling is used as a default assumption;

Group C: Genotoxic carcinogens - for which a practical threshold is supported; and

Group D: Non-genotoxic carcinogens and non-DNA reactive carcinogens - a true threshold may be established associated with a NOAEL.

SCOEL seeks to derive health-based OELs for carcinogens in Groups C and D and, if possible, apply risk-based assessments to Category A and B substances (Bolt & Huici-Montagud, 2008; Bolt et al, 2004; EC, 2013).

2.1.3 Additional notations

In addition to recommending an 8hr TWA and 15 min. STELs, OEL-setting committees also use additional notations, where appropriate, to assist in risk management decisions; these include, skin notation, respiratory sensitisation and noise. In the case of the latter notation, there is evidence that demonstrates a link between certain organic solvents and excessive noise in the workplace, leading to hearing loss in workers (Unlu et al., 2014).

3. Occupational exposure to manganese

The world-wide mine production of manganese ore was estimated by the US Geological Survey to be around 18 million metric tonnes in 2014. Of that, 61% was produced in the Gabon, 16% in Australia, 14% in South Africa, 4% in Ghana, and 5% in a number of other countries (USGS[5]).

The main uses of manganese continue to be for the production of alloys (ferrous and non-ferrous), particularly in the steel making industry, and it is estimated that around 89% to 94%

[5]US Geological Survey (USGS);http://minerals.usgs.gov/minerals/pubs/mcs/2015/mcs2015.pdf

of manganese ore is used as feedstock for manganese alloys (CPM, 2011). The remaining manganese ore is used in foundry and welding, accounting for less than 10% of manganese ore (CPM, 2011). It is estimated that 6% to 11% of manganese ore is used in the production of electrolytic manganese metal (EMM), electrolytic manganese dioxide (EMD), lithium manganese oxide, manganese sulphate, and other chemicals. As noted above, the key metallurgical uses of manganese are in steel, aluminium and copper, while the key non-metallurgical uses of manganese are in batteries and agricultural feed and fungicides.

A review of workplace exposure to manganese was carried out by the Institute of Environment and Health (IEH) in 2004, and reported within a Criteria Document[6] produced for the International Manganese Institute (IMnI). The review found that there was substantial variability in exposure levels to manganese both between and within individual industry sectors. The three sectors for which most data were available were mining, manganese metal and alloy production and battery manufacture. The highest and most variable exposures were in mining with a maximum concentration (arithmetic mean) of 114 mg/m^3 as manganese in total dust reported for miners in an Iranian study (Boojar and Goodarzi, 2002). In comparison, the highest exposure concentration reported in a study of South African miners in a modern mine was 1.5 mg/m^3 (Myers et al., 2002). These two studies, although contemporaneous, show very large differences in exposure levels. This must be largely due to differences between modern high technology mining operations using efficient control measures, such as use of water sprays, good ventilation, and isolation of workers from sources of dust, and

[6] Available at: http://www.iehconsulting.co.uk/IEH_Consulting/IEHCPubs/HumExpRiskAssess/w17.pdf

what must be assumed to be older, less controlled methods of extraction. Some high exposures were also reported for manganese metal and manganese alloy production with a maximum exposure concentration of 27 mg/m^3 (inhalable) reported in a Norwegian smelter (Johnsen *et al*. 2010) though typical levels were much lower (geometric mean = 0.254 mg/m^3). Exposure concentrations associated with battery manufacture ranged up to 11 mg/m^3 as inhalable manganese in a Belgian study (Roels et al., 1992).

Importantly, the IEH review (IEH, 2004) specifically examined information about the concentrations of manganese in different size fractions, to derive conversion factors that could be used to assist in the interpretation of epidemiological studies in which different fractions of manganese in air had been measured (respirable, inhalable or total dust). The authors concluded that only a small proportion of inhalable manganese was of respirable size, although this varied by process (with exception of welding). A conversion factor of 1.2-3.2 was proposed to convert 'total' to 'inhalable' concentrations and a factor of 0.1-0.5 to convert 'total' concentrations to equivalent 'respirable 'concentrations (to allow cross study comparison).

The IEH review (IEH, 2004) also assessed the limited biological monitoring data that was available at the time of publication. The data showed considerable interindividual variability in blood manganese levels, although manganese exposed workers generally had higher blood manganese than unexposed. The data did not however, establish a clear relationship between exposure concentrations of manganese in air and blood manganese, and there was little evidence to support the use of blood manganese as a reliable exposure index. Over the range of studies reviewed, urinary manganese levels also varied substantially, even among the controls, however, almost all of the studies reported significant differences between controls and exposed workers. No clear relationship between airborne exposure and urinary levels on an individual basis was demonstrated.

3.1 OEL setting for manganese

In their review of the literature regarding occupational exposure to manganese in 2004, the IEH proposed OELs of 0.1 and 0.5 mg Mn/m^3 for respirable and inhalable fractions respectively. Consideration of the levels and duration of exposure in the studies by Gibbs et al. (1999) and Myers et al. (2002), which found no neurological effects in exposed workers, and the study by Roels et al. (1992), which showed adverse neurological effects, was used as a basis for determining a NOEL and the proposed OELs; these were considered protective based on knowledge at the time.

However, an updated search of studies and reviews around the exposure and uptake of manganese and of neurotoxic effects in workers, published subsequent to the IEH 2004 review (as detailed in Appendix A), suggest that some non-clinical neurofunctional adverse effects may be occurring around the OELs proposed by the IEH 2004 review.

3.1.1Availability of robust exposure data

For OEL setting, as in all risk assessments, often the weakest component of key occupational studies for manganese has been the exposure assessment, which is as important a consideration as the toxicological health outcome. For manganese, cross study comparisons of data also remain limited by the variable approach taken to sampling by the authors.

A number of investigators have reported exposure measurements for the respirable, total/inhalable or other size fractions of manganese which are expected to have different bioavailabilities (ATSDR, 2012). The particle size of inhaled manganese would be anticipated to affect uptake and distribution and it is conventionally assumed that a much higher absorption of inhaled material in the respirable fraction is deposited in the lungs than of coarser material, which is largely swallowed. Several studies provide information about particle size in individual workplace environments (Ellingsen *et al*., 2003; Harris *et al*., 2005; Pearson and Greenway, 2005; Berlinger *et al.,* 2007; Michalke *et al*., 2007; Berlinger *et al.,* 2008; Ellingsen et al., 2008; Ross *et al*., 2009; Keane *et al*., 2010; Lehnert *et al*., 2012). As would be anticipated, there are substantial differences in the size distribution of airborne manganese in different workplace environments with processes that generate fume giving rise to aerosols with a much higher respirable content (as a percentage of total/inhalable manganese) than activities such as breaking up ore or cutting manganese containing materials. However, the ratio of respirable to inhalable Mn in workplace air is generally in the range 0.1-0.5.

A further issue for manganese regarding exposure monitoring methodology is the unexplained variability observed in mean blood manganese levels reported for non-exposed controls in workplace studies, as well as in studies of the general population. Currently, therefore, it is not clear whether real differences in mean blood manganese levels exist between different population groups; potential causes for such differences could include factors such as dietary intake of manganese and iron. Alternatively, the differences may arise from differences in measurement protocols, including the sampling regimes adopted by the authors as it was notable in the identified literature that the validated NIOSH methods for metals in urine and blood were not widely used.

Significant exposure via the skin is unlikely in most workplaces where manganese is present as the nature of the tasks being undertaken means that workers are likely to be wearing gloves and protective clothing and there is limited potential for direct skin contact to occur. Inadvertent ingestion is most likely to arise in individuals with poor personal hygiene, particularly where there are no strict procedures to ensure that workwear is removed and exposed skin washed prior to breaks in the working day and at the end of the work shift (IEH, 2004).

3.1.2 Assessment of available neurotoxicity data

In their review, the IEH (IEH, 2004) noted that the available evidence at the time of publication indicated that subtle subclinical neurological effects in humans were the most critical endpoint associated with chronic low-level occupational exposure to manganese. This is suggested to be linked to the accumulation of manganese in brain tissue following inhalation, with the basal ganglia region being a primary target of toxicity. These changes were, and still are, considered a suitable basis for setting an OEL. Indeed there is a reasonable body of evidence from human cohort studies that occupational manganese exposure may induce subtle neurotoxic changes and that current occupational levels of manganese may be associated with the onset of some symptoms of manganism (EC, 2011; ATSDR, 2012).

Whilst there is a growing body of evidence that occupational exposure to manganese at levels below those associating with the onset of manganism may elicit subtle neurofunctional perturbations (Meyer-Baron et al., 2009 and 2013), such changes are only detectable using specialised testing and represent sub-clinical effects. Studies that support the existence of such an association are subject, to varying extent, to methodological limitations. However, recent work has strengthened the evidence base that there is a lack of progression (or, in some cases, regression) of the subtle changes once the occupational exposure is reduced or stopped (Bouchard et al. 2007b and 2007c; Wastensson et al, 2012). Furthermore, there is now a possible explanation for the varying levels of recovery observed, with evidence suggesting that different brain loci may show varying degrees of susceptibility and recovery potential (Bowler et al., 2011).

Many of the studies that have been reported since the IEH review (IEH, 2004) have sought to use those neurofunctional tests that appear to be particularly sensitive at identifying the subtle neurological changes thought to associate with manganese toxicity. These recent studies have, however, continued to be limited to a significant extent by continued reliance on cross-sectional designs and also by use of potentially unreliable exposure estimation methods. Consequently the strength of the potential association between manganese exposure and these subtle subclinical cognitive or neuromotor changes is still poorly characterised and the relevance of these minor differences in terms of either their clinical or quality of life consequences remains unknown (SCOEL, 2011; ACGIH, 2013).

3.2 Current and proposed OELs for manganese

Since the OELs were proposed in the review by the IEH (IEH, 2004) there has been much activity around the setting of OELs for manganese by a number of the key OEL setting bodies. In addition, the EU SCOEL has published recommendations for OELS for manganese and its inorganic compounds[7]. Table 1 shows current OELs from the OEL setting bodies, with the OELs proposed by the IEH in 2004 included for comparison. It should be noted that the recent evaluations of the SCOEL, MAK and the ACGIH suggest that it may be possible to establish reliable health-based OELs for neurofunctional changes which can be considered true NOAELs for these effects.

[7]It should be noted that at the time of writing, this recommendation has not yet passed though the EU DG Employment, Social Affairs and Inclusion's appropriate committee procedures and thus, it is not known whether the document and its recommended OELs will be accepted or modified.

Table 1. Current and proposed OELs for manganese

	Respirable OEL (mg Mn/m^3)	Inhalable OEL (mg Mn/m^3)
IEH (2004)	**0.1**	**0.5**
OEL Setting Committees		
SCOEL IOELV (2009 - 2011)	**0.05**	**0.2**
MAK Commission (2010)	**0.02**	**0.2**
ACGIH TLV-TWA (2011 - 2013)	**0.02**	**0.1**

IEH – The Institute of Environment and Health; SCOEL – The Scientific Committee on Occupational Exposure Limits; IOELV – indicative occupational exposure limit value; MAK - Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (Germany); ACGIH - The American Conference of Governmental Industrial Hygienists ; TLV-TWA - Threshold Limit Value–Time-Weighted Average.

The derivation of each of these OELs is discussed below, with details of individual studies given in Table 2.

3.2.1 The Scientific Committee on Occupational Exposure Limits

The Scientific Committee on Occupational Exposure Limits (SCOEL) recommendations note that there is a substantial literature on the effects of manganese on the human nervous system and that high exposures can result in severe neurotoxic signs and symptoms, some of which resemble those of idiopathic Parkinson's disease. It concludes 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. However, it noted that more recently, several studies on lower occupational exposures to manganese have reported less severe, subtle, non-clinical neurofunctional 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.

In their findings, SCOEL state that it was not possible to identify one study on which to base the IOELVs as the data is highly heterogeneous (e.g. different types of industry, different manganese compounds and particle sizes, different study designs and different neurofunctional measurements). They recommended a global approach using the most methodologically-sound studies (i.e. showed adverse neurological effects and identified a point-of-departure (POD) in the dose-effect/response relationship), as used by IEH (2004). The SCOEL Recommendation, based on studies by (Roels et al., 1992; Gibbs et al., 1999; Myers et al., 2003; Young et al., 2005; Bast-Pettersen et al., 2004; Ellingsen et al., 2008; Lucchini et al. 1999 in HC, 2008) was thus as follows:

"A reasonable **respirable IOELV of 0.05 mg/m^3** can be recommended, and a reasonable **inhalable IOELV of 0.2 mg/m^3** 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".

SCOEL are thus drawing attention to the fact that these recommended values were highly precautionary and would protect against any neurofunctional change. Indeed, SCOEL noted that the changes reported are subtle early neurofunctional effects which are non-clinical in nature and are only detected at a statistical level between groups of workers. In addition, some of the subtle neurofunctional effects of manganese on the CNS are reversible although the degree of reversibility has not been defined.

In addition to these airborne IOELVs, SCOEL agreed with the views on biological monitoring in the 2004 CD (IEH, 2004) on which the SCOEL/SUM is mainly based. That it was not possible to recommend a health based biological monitoring standard due to the poor correlation between airborne manganese and either blood or urine concentrations of manganese. However, they noted that 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 (95thpercentile) not occupationally-exposed to manganese, but of working age (EC, 2011).

3.2.2 The Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area

The Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) in Germany revised their MAK values for manganese and its inorganic compounds in 2010. They followed the recommendations of the IEH (IEH, 2004) with regards to setting values for both respirable and inhalable fractions.

Although a comprehensive evaluation, they noted that "as toxic effects on the airways and lungs (so-called manganese pneumonia) after repeated exposure to manganese are not induced below concentrations of at least 1 mg/m^3 (IEH 2004), its neurotoxic effects will be used for derivation of the MAK value". They thus concentrated almost entirely on human neurofunctional investigations and classified these studies into those to be considered for OEL setting, for inhalable and respirable fractions separately, which met the following criteria (Category A studies): exposure to manganese at the workplace by inhalation, application of standardised neuropsychological test procedures, parallel investigation of a non-exposed control group, valid data on manganese concentrations in the ambient air, as well as the control of major confounders. Studies that did not meet all criteria were assigned as Category B, with studies of welders assigned to Category C. The derivation of the MAK value was established on the basis of studies in Category A, with those in Categories B and C used as supporting evidence (Chia *et al*., 1993; Lucchini *et al*., 1999; Mergler *et al*., 1994; Gibbs *et al*., 1999; Young *et al*., 2005; Myers *et al*., 2003; Bast-Pettersen *et al*., 2004; Meyer-Baron *et al*., 2009).

As with other recently-active OEL-setting committees, the MAK considered that the most sensitive endpoint for deriving workplace threshold concentrations for manganese was the occurrence of preclinical neurotoxic effects after inhalation. They examined in detail exposure with measurements in motor and cognitive function and looked for concordance between studies. For the derivation of a MAK value based on neurofunctional toxicity data, the MAK stressed that it needs to be shown that (a) no single effect is involved in only one study, (b) different studies provide evidence of a similar effect at comparable dose ranges, (c) the observed performance impairments are compatible with the proposed neurotoxic mechanisms and (d) the impairments in performance observed can be seen as indicators of clinical changes in exposures either extremely high or lasting for many years. If these prerequisites are met in the case of manganese, the impairments in performance are to be classified as adverse effects, as they constitute early signs of clinically-relevant changes.

They also stress that in deriving a MAK value from epidemiological cross-sectional studies, unlike animal investigations, no direct derivation of a NOAEC or LOAEC is possible, as only an average value is available for manganese exposure in the exposed group.

3.2.3 The American Conference of Governmental Industrial Hygienists

The American Conference of Governmental Industrial Hygienists (US ACGIH) have had a number of Draft notices of intended changes (NIC) for manganese, elemental and inorganic compounds, published over the last few years, with a final accepted version being published in 2013 (ACGIH, 2013). It is important to note that ACGIH also propose both respirable and inhalable values.

In the development of their recommendations, the ACGIH first cite the study by Roels *et al*. (1992) which proposed that a respirable OEL of 0.036 mg Mn/m^3 would protect most workers from neurological effects. Further analysis of this study data by the ATSDR (ATSDR, 2012) using a benchmark dose approach, allowed the ACGIH to calculate a $BMDL_{10}$ of 0.07 mg Mn/m^3 as a NOAEL.

In their recommendation, the ACGIH also noted the analysis by Crump and Rousseau (1999) of the follow-up study by Roels (1987) which showed that after 11 years further exposure to Mn, there was some evidence that the previously reported sub-clinical neurological effects were not progressing. Next, they cited the study by Mergler *et al*. (1994) in which workers were exposed to a median level of 0.032 mg Mn/m^3 (respirable). The workers in this study were examined 14 years *following cessation* of exposure and it was noted that some of the previously reported neurobehavioural changes were still persisting (Bouchard *et al*. 2007a and b). The study by Lucchini *et al*. (1999) showed an LOAEL for neurological effects of about 0.1 Mn/m^3 (total dust) after an average of 11.5 years. This corresponded to a respirable geometric mean concentration of 0.036 mg Mn/m^3.

The ACGIH noted that the Bast-Pettersen *et al*. (2004) study reported tremor (impaired hand steadiness) at a geometric mean level of 0.036 mg/Mn/m^3 (respirable), whilst in a study on South African manganese smelters, Young *et al*. (2005) showed increased neurobehavioural changes in workers exposed to 0.01-0.04 mg Mn/m^3 (respirable).

In developing the rationale for their TLV, the ACGIH noted that the LOAELs for neurological effects derived from the studies of Bast-Pettersen *et al*. (2004), Lucchini *et al*. (1999), Mergler *et al*. (1994) and Roels *et al*. (1992) which are respectively, 0.036, 0.032, 0.038 and 0.036 mg Mn/m^3 (respirable) are in close agreement. Thus, **a TLV-TWA of 0.02 mg Mn/m^3 respirable particulate matter** was recommended for manganese and its inorganic compounds "to reduce the potential for preclinical, neurophysiological and neuropsychological effects in manganese-exposed workers." It was noted by the ACGIH that this value is 1.5-2.0 times lower than the range of LOAELs observed.

However, the ACGIH also stated that in some occupational situations, exposure to manganese was to aerosols with a substantial fraction greater than 4 µm MMAD (respirable range) and thus a supplementary TLV-TWA of 0.1 mg Mn/m^3 inhalable particulate matter was recommended for conditions where particles >4 µm are anticipated. They note that the ratio of inhalable to respirable mass may vary from 1:1 to 10:1 but, have used a midpoint ratio for conversion of 5;1, and cited the previous IEH Criteria Document (IEH 2004), which also gave this ratio, in support of their approach. They finally note that if the inhalable TLV-TWA is used, then this should be *in addition* to the respirable TLV-TWA.

3.3 Assessment of key studies used for derivation of OELs

As discussed previously, often the weakest component of key studies has been the exposure assessment, which is as important as the toxicological health outcome. In the case of occupational exposure to manganese and its inorganic compounds, usually the neurofunctional tests although very variable and many without defined normative data, have been reasonably well described and with the use of appropriate control groups. However, in many cases the studies have contained unreliable estimates of long-term exposure often based upon limited exposure data.

An outline of the studies that have been included in the derivation of OELs by the IEH (IEH, 2004) and the OEL setting bodies, SCOEL, MAK and ACGIH is given in Table 2. In assessing these studies, one of the key considerations must be the reliability of the exposure assessments undertaken and what influence that may have on the overall OEL.

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Table 2 Critique of exposure assessment in studies consideredby OEL setting committees to derive OELs for manganese and its inorganic compounds

Study Author	Included in OEL derivation	Comments on Exposure Assessment
Lauwreys *et al*., 1985	IEH 2004	Only current (not historical) exposure data available. Exposures ranged from 1-19 years (mean 7.9), 8 hour TWA ranged from 0.07-8.61 mg/m^3 (arithmetic and geometric mean values 1.33 and 0.94 mg/m^3 respectively) – 80 samples – authors indicated that past exposures may have been lower as production rates were lower (however industrial hygiene has generally improved through time), fertility effects only examined for exposed group as a whole, not in relation to relative current exposure levels or any sort of cumulative exposure index (CEI). ***Critique: study considered not helpful to establishing an OEL.***
Roels *et al*., 1992	IEH 2004; EC 2011; ACGIH 2013	Personal measurements of respirable and inhalable exposures to Mn. Inhalable measurements based on grit pots in cyclone samplers which is not an approved sampling method. Cumulative exposure estimated on basis of current exposure levels and job history - some potential to under-estimate cumulative exposure, if exposures were less well controlled in the past however, specific statement to effect that work processes have not been modified over previous 15 years is included and measurements would therefore be expected to be representative of past exposure. Exposure response relationship illustrated for lifetime cumulative exposure as a continuous variable in a non-threshold model, and also for exposure categorised as <600, 100-1200, >1200 ug Mn/m^3.years with apparent effects in <600 group - nothing to pinpoint a threshold. The upper bound estimated ED05 level of the investigated endpoints were 3575 ug Mn/m^3.year total and 730 ug Mn mg/m^3.year respirable - these levels are subsequently described as threshold for effects. ***Critique: study did not use an approved sampling method which may impact on exposure estimates.***
Mergler *et al*., 1994	ACGIH 2013	Static samples at 13 representative locations through facility, sampling and analytical procedures described, no QC details – may not be closely related to actual personal exposure; total and respirable Mn measured. Only 38 samples were collected – not many to characterise exposure across workplace and no evidence that investigators tried to establish levels of exposure associated with different job functions. It is stated that dust levels had previously been much higher.

		Critique: the relationship between MnAir and neurobehavioural effects does not appear to have been investigated and the study is not helpful to the setting of an OEL
Gibbs *et al*., 1999	IEH 2004; EC 2011	Current (1997) respirable and total concs of Mn were measured for 12 job categories (not given) and arithmetic mean used to estimate pre-1997 exposure levels for each job category, taking account of process and work practice changes and the results of 15 minute compliance samples collected before and after such changes. Job histories derived from personnel records, interview and pay roll records and used to calculate cumulative exposures. The sampling and analysis procedures are described but no QC information provided. The number of samples collected does not appear to be stated and there is no information about the variability of the exposure estimates for each job category. There is a small uncertainty around the back projection of exposure concentrations from 1997 measurements – possibility that past exposures could be under-estimated. Results of neurobehavioural tests assessed against previous 30 days, years and lifetime exposure – treated as continuous variable – no artefacts associated with grouping of exposures. ***Critique: It is not certain how much confidence to ascribe to the exposure estimates.***
Lucchini *et al*., 1999	IEH 2004; EC 2011; Health Canada 2012; MAK 2010; ACGIH 2013.	Air sampling performed 1 month before neurobehavioural testing, respirable and total Mn concentrations determined using personal and stationary sampling – methods are described, no QC details, Cumulative exposure index (CEI) calculated by multiplying average annual airborne Mn concentration characteristic of each job performed by the subject during his work history and years exposed with adjustment for inhalation rate for different task workloads. No adjustment made for any changes in work practice – possible that measured exposures would be less than historic exposure concentrations. MnB and MnU determined for samples collected at time of nuerobehavioural test. Plot of CEI and MnB indicates an apparent relationship – no information is provided as to the relationship between CEI and current exposure levels or MnB and current exposure levels. ***Critique: the neurobehavioural test results are not analysed in relation to MnAir or CEI, so the paper is not informative about the exposure levels that give rise to effects versus those that don't – some effects seen in a group with current exposures that range from 0.026-0.75 mgm-3 as total Mn. Unlikely to be helpful in setting an OEL.***
Crump & Rosseau , 1999	IEH 2004	No Mn Air data and results not assessed in terms of cumulative exposure to Mn – could be assumed that air Mn concentrations similar to those described by Roels et al., in earlier study at same plant. ***Critique: overall not helpful to setting an OEL – confirms previously described levels of exposure at plant have adverse effects but not enough to derive a NOAEL or LOAEL.***

Myers *et al*., 2002	IEH 2004	Base-line cross-sectional study in miners working in deep mining and opencast. Largest study, modern technology. Well conducted and described. Inhalable fraction = 1.4 times total dust. No correlation between MnA andMnB. ***Critique: good quality exposure data recorded.***
Clewell *et al*., 2003	ACGIH 2012	Calculation of BMD for datasets underlying Roels et al., (1992) and Gibbs et al., (1999) studies. Some approximations required to derive exposure concentrations for individual workers. Analysis based on current exposure concentrations (based around arithmetic mean), given the likely interindividual variability in exposure in each exposure group, there could be significant under or overestimates of exposure at an individual level) – CEI was not investigated (which seems a major weakness). ***Critique: the elegance of presentation hides considerable uncertainty in the most appropriate way to handle the exposure data.***
Myers *et al*., 2003a	EC 2011;	Exposure assessment based on measurements made to meet regulatory requirements with some additional measurements made to confirm reliability of routine measurements. NIOSH methods of analysis - no detail on QC but no reason to anticipate that data would not be reliable. Measurements made for individuals representative of task being assessed - data collected over 4 years - should have a reasonable long term average TWA for each occupational group. Individual mean and cumulative exposure assessments made by multiplying concentration for each job times years worked in that job and average exposure intensity and average exposure intensity calculated from cumulative exposure divided by service life. Exposure treated as a continuous variable in analysis of exposure-response relations. ***Critique: unsure how representative measurements are of historical exposure which may have been higher.***
Myers *et al*., 2003b	MAK 2010;	Analytical methods and QC well described, but time period over which sampling conducted not given. ***Critique: implication that exposure assessment based on a snapshot of exposure concentrations rather than being representative of long term mean exposure levels.***
Bast-Pettersen *et al*., 2004	ACGIH 2013; EC 2011	Mn Air - personal full shift sampling for 3 days for each individual on days close to their neuopsychological examination. No information about long term variation in individual exposure levels. Urine and Blood samples taken. Exposure data treated as continuous variable. Plots of data as groups with differing duration of exposure. Data examined against low, medium and high MnB. ***Critique: exposure data may be unrepresentative of past exposures - potential for effects of exposure to low concentrations to be over-estimated.***

Young *et al*., 2005	BD 2013; EC 2011; ACGIH 2013	Related to Myers (2003b) smelter study - not sure whether same source of exposure data. 310 inhalable dust concentrations, 98 personal dust concentrations - suspect single measurement campaign - not clear whether representative of historical exposure levels - cumulative exposure indices developed but then divided by duration of exposure to give average intensity. Study focussed on respirable Mn - estimation of respirable Mn where gaps in job exposure measurement. Link given to more detailed description of how exposure estimates were derived is broken. ***Critique: response examined by exposure category by average intensity of exposure rather than cumulative exposure - so issue of whether central tendency, upper or lower bound concentration most relevant plus issues of whether cumulative exposure and/or peak exposures more relevant. Authors state that only the intensity groupings presented as cumulative exposures gave similar results - which seems surprising.***
Ellingsen *et al*., 2008	EC 2011	Details of sampling and analysis in Ellingsen et al (2006). Sampling conducted as a single survey- blood and urine samples for 96 welders - 180 air samples collected on preceeding 2 days for each welder providing biological samples, QC for analysis described, evidence of a methodological approach to the sampling. ***Critique: no information about day to day variability of the exposure of any individual - measurements reflect average for group; analysis examined MnB, MnAir and duration of exposure but not cumulative exposure. Exposure data may be unrepresentative of past exposures - potential for effects of exposure to low concentrations to be over-estimated. No information that would confirm MnB, MnAir for individuals that were used in the analysis were actually representative of long term exposure for those individuals. The study tells you about the average level of neurobehavioural impairment versus an average cumulative exposure as MnAir but is not going to provide reliable dose-response information beyond that - the determination of MnAir, however, is likely to be reliable***.
Meyer-Baron *et al*., 2009 (meta-analysis) 13 studies included: Bast-Pettersen *et al*., 2004 Blond &Netterstrom, 2007; Blond *et al*., 2007	MAK 2010	 See above No details given of how Mn measurements made. Dust measurements made in 1970s varied from 0.7-62.2 mg/m^3 as total dust, Mn 1-3%, Mn in air assumed to have been between 0.01 and 1.9 mg/m^3, median 1.1 mg/m^3. Personal and static measurements of Mn made in 1990s - personal inside airfed helmets, static outside, much higher, stated that

		compliance with use of air fed helmets was <100% - total Mn 0.01-0.84 mg/m^3, median 0.03. Median PbB in 1989 was 0.79 umol/l = <2 ug/dL. ***Critique: comparison made between exposed and unexposed groups - no exposure response information in terms of threshold of effects, contribution of higher levels of historical exposure or consideration of cumulative exposure.***
Chia *et al*., 1993		Regular annual monitoring of exposure had been undertaken for many years – personal samples for a representative selection of workers. Neurobehavioural effects not considered in relation to airMn or CEI – air monitoring results show steep decline in air Mn through time – so workers received historical exposures that were vastly greater than those experienced at the time of the study. ***Critique: study not informative about relationship between air Mn and neurobehavioural effects.***
Ellingsen *et al*.,2008		See above
Lucchini *et al*., 1997		Exposures quoted as total dust. No differentiation by job function or location reported. ***Critique: Well-conducted study but small sample size and lacking detail.*** .
Mergler *et al*., 1994		See above
Myers *et al*., 2003a		See above
Roels *et al*., 1992		See above
Roels *et al*., 1987		Cumulative exposure unable to be accurately estimated. Exposure categories derived from supervisors estimations of past exposure. There was a significant rank correlation between this subjective estimation of cumulative exposure and blood manganese levels but not urinary levels. On an individual basis, neither blood nor urinary manganese correlated with current exposure or with duration of exposure. ***Critique: Well-conducted study with some indication of adverse effect of Mn exposure on respiratory system; however, respiratory findings not backed up in Roels et al., 1992.***
Sjögren *et al*., 1996		Exposure assessment based on exposure times provided by Welders and the reported time spent on TIG or MIG welding - the welders appear to have been questioned some years after exposure - only 13 welders had been exposed to Mn and had welded for more than

		100 hours in high alloy Mn steel - small information base. Exposure to particles in breathing zone of welders measured in mid 1970s was 10 mg/m^3 for MIG and 1 mg/m^3 for TIG - fumes from electrodes used contain 2-8% Mn. Study focussed on biological monitoring - no relationship between MnB and former Mn exposure. Exposure response relationship reported for Al. ***Critique: no detailed investigation of exposure response relationships reported and no clear information provided about the levels of Mn exposure that were associated with neurobehavioural impairment.***
Wang *et al*., 2006		Details of exposure measurements not given – not clear whether personal measurements of whether respirable or total (welding so probably predominantly respirable anyway); routine surveillance data from 1995-2002 showed concs of Mn ranging from 0.1-0.5 mgm-3. ***Critique: effects not looked at in relation to air Mn – probably not helpful in setting an OEL.***
Yuan *et al*., 2006		20 air samples were collected during welding – 10 minute samples collected at height of breathing zone – implies not true personal samples - particularly as welders would have been wearing helmets – from these samples cumulative Mn exposures were calculated based on exposure duration – given the small number of measurements on which these estimated cumulative exposures are based, there is considerable uncertainty in their reliability. It is not stated how 8 hour TWAs were assessed on the basis on ten minute measurements. ***Critique: although the study establishes neurobehavioural effects in the exposed workers (with an estimated mean exposure level) it does not provide information as to the level of exposures associated with NOAELs and LOAELs – neurobehavioural endpoints are not analysed against air Mn or CEI.***

From the critique of available exposure assessments carried out for the studies utilised by SCOEL, MAK and ACGIH, it is possible to identify the key studies *based on reliability of the exposure data* (although it should be noted that some have other remaining limitations) as those reported by Roels et al. (1992), Gibbs et al. (1999), Myers et al. (2003a), Bast-Pettersen et al. (2004) and Ellingsen et al. (2008).

An important limitation of the above studies is a lack of standardisation of some test methodology to identify response/effects, especially subtle non-clinical neurotoxicological effects. For others with standardised methodologies, the interpretation of results can be subjective. The main finding(s) from the neurological testing carried out as part of the above studies is detailed in Table 3.

Table 3 Outcome of neurological testing in key studies.

Study	Occupational Group	Neurological testing	End-point
Roels *et al*., 1992	Battery workers	• audioverbal short term memory test. • simple visual reaction time measurement over 4 x 2 minutes using a chronoscope (EAP, Issy-les-Moulineaux, France). • hand steadiness test (3 x 7 holes, 15 seconds per hole, hole diameter 8 to 3-5 mm) using the hole tremormeter • eye-hand coordination test (2 x 1 min) using the orthokinesimeter of the apparatus of Bize (EAP, Issy-les-Moulineaux, France). The last three tests were performed with the dominant hand only. For the eye-hand coordination test the subject was requested to perform the test at a	Decline in visual reaction time,eye-hand coordination, hand steadiness. LOAELs of: 0.22 mg/m3 (resp) 0.95 mg/m3 (total) Based on increased risk of hand tremor. Logistic regression LOAELs: increased risk of peripheral tremor (5% abnormal response increment) when the lifetime integrated exposure to: respirable manganese dust exceeded 3.575 (p=0.029) and to total

Table 3 Outcome of neurological testing in key studies.

Study	Occupational Group	Neurological testing	End-point
		speed imposed by a metronome (1 hit/s).	dust exceeded 0.730 mg/m³ x years (p=0.054).
Gibbs *et al.*, 1999	Smelters	• hand steadiness (movemap steady; movemap square; EAP tremometer) • Hand-eye co-ordination (EAP Orthokinisimeter) • Rapidity of motion (4 choice reaction time; finger tapping) • mood and neuropsychological healh questionnaire.	NOAELs of: 0.04 mg/m3 (resp) 0.11 mg/m3 (total) Based on lack of neurobehavioural changes at this level of exposure.
Myers *et al.*, 2003a	Miners	• Maximum forward digit span • Maximum backwards digit span • Digit symbol score • Mean reaction time.	NOAEL of: 0.2 mg/m3 (total) based on lack of neurobehavioural changes at this level of exposure.
Bast-Pettersen *et al.*, 2004	Smelters	• Neuropsychiatric questionnaire. • Wechslers adult intelligence scale. • Digit Symbol. • Trail-making test. • Stroop test. • Digit Span. • Benton test. • Kløve-Matthews Motor Steadiness battery. • Tremor test. • Finger Tapping. • Foot Tapping. • Dynamometer. • Grooved Peg-board test. • CATSYS System. • Luria-Nebraska Thumb/Finger Sequential Touch. • Simple Reaction Time test. • Hand Eye Coordination test.	LOAELS of: 0.036 mg/m3 (resp) 0.301 mg/m3 (inhal) Based on hand tremor.
Ellingsen *et al.*,2008	Welders	• Questionnaire Q 16. • Digit Symbol. • Digit Span. • Finger Tapping. • Foot Tapping.	LOAELs of : 0.338 mg/m3 (respirable) 0.423mg/m3 (total) NOAELs of: 0.110 mg/m3 (respirable)

Table 3 Outcome of neurological testing in key studies.

Study	Occupational Group	Neurological testing	End-point
		• Dynamometer. • CATSYS Postural Sway test. • CATSYS Maximum Frequency test. • Kløve–Matthews Static Steadiness test.	0.137 mg/m3 (total) Based on impaired finger Tapping speed

For some of the neurofunctional tests used in the above investigations there are clear NOAELs and for others there are LOAELs. In the case of LOAELs it is sometimes difficult to appreciate what the significance of the functional outcome may be, as all the findings are considered sub-clinical at worst. This is further complicated by the fact that for many of these neurofunctional tests (e.g. eye-hand coordination) there is little or no normative data in order to give any changes seen in some of these studies a 'real-life' context. Where such data does exist, such as for visual reaction time, the significant differences in mean RT between control and exposed groups noted in the study by Roels *et al*. (1992) are well below those seen with aging (Spreen et al., 2006). It is therefore difficult to judge whether the non-clinical effects for visual reaction time described by Roels et al. (1992) would impact on the quality of life of exposed workers.

4. Conclusions

The evidence base described above highlights the continued concerns that exist with regard to several potential adverse health effects that may occur following occupational exposure to manganese and its inorganic compounds. However, as previously discussed, the most critical effect for humans associated with chronic low-dose occupational exposures remains some subtle non-clinical neurological changes in neuromotor and cognitive functions (shown by endpoints of tests associated with motor speed and speed of information processing). These are considered to be the lead effects since they are detectable at the lowest occupational exposure scenarios available. Hence, any health-based OEL based on these endpoints will be fully protective against any other possible health effect. It should be noted however, that interpretation of such subtle changes may be subject to variability both between tests and within study groups, making precise judgement of associated exposure levels difficult.

Although all the reviewed studies relating to neurological changes in workers have concluded that the effects are subtle and non-clinical in nature, it is apparent that there has been a tendency across regulatory guideline-setting bodies to establish somewhat lower OELs than those proposed in the review by the IEH (IEH, 2004); this applies to both inhalable and respirable fractions. The recent OELs proposed by the ACGIH in 2013, the SCOEL in 2011 and the MAK in 2010 are health-based in nature and relate to establishing a level at which no effect, even if extremely subtle in nature, would be anticipated to occur over a working lifetime of 40 years; i.e., they are essentially derivations of a NOAEL.

Additional evidence from a few new longitudinal investigations has reinforced the suggestion that subtle neurological effects detected in some repeated studies may not progress once exposure has ceased or been reduced. However, it is now clear that not all changes are fully reversible once established.

There is still some question as to the significance of the small non-clinical neurological changes seen in exposed workers regarding their consequences in terms of both human health and well-being. That is, it remains unclear if they represent key early markers of an increased risk of developing more serious neurological disorders (including manganism) in later life or if they are of little or no consequence to the individual worker.

Based upon the overall evidence base, it is concluded here that the 8-hr time weighted averages (TWA) for respirable and inhalable fractions as recommended by the SCOEL in 2011 are the most methodologically-sound, as they are based on the best available studies most suited to the development of health-based OELs for both respirable and inhalable fractions. The dose-response characterisation informed by the studies used can be considered to establish a true human NOAEL for all the neurofunctional endpoints examined in the selected studies. There is no requirement for short-term exposure limits and as noted in the review by the IEH (IEH, 2004), there is no reliable biological exposure limit that can be recommended either based on a health effect or equivalence to an airborne exposure. However, research is underway to validate useful specific biomarkers of exposure to manganese, in particular for recent exposure.

It should be noted that as these recommended OELs are based on very subtle neurofunctional perturbations which represent the earliest detectable, potentially adverse changes arising from occupational exposure to manganese adherence to the proposed OELs will therefore provide protection to workers from all of the other reported effects of occupational exposure to manganese and its inorganic compounds. However, it is also important to highlight that although the recommended OEL will provided protection to all workers, workers in different fields – alloying, battery production, fertiliser production, mining, welding etc., could be protected with less stringent OEL's as the valency, toxicokinetics, solubility, bioavailability of different inorganic manganese based substances are not the same. Although this lends itself to the concept of setting 'sector-specific' OELs, data is insufficient at the present time for the derivation of pragmatic OEL's for each working group sector.

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Appendix A - Literature search strategy

Web of Science

TOPIC ("BaMnO4" OR "KMnO4" OR "FeMn" OR "Mn2O3" OR "Mn3O4" OR "Mn3O7" OR "Mn5O8" OR "Mn(NO3)2" OR "Mn(SO4)2" OR "Mn2(SO4)3" OR "MnCl2" OR "MnO" OR "MnO2" OR "MnSO4" OR "Na3MnO4" OR "SiMn" OR siliconmanganese OR "manganous salt*" OR braunite OR cianciulliite OR hausmannite OR polianite OR pyrochroite OR pyrolusite OR ramsdellite) AND **TOPIC** (toxic* OR exposure* OR manganism OR parkinson* OR poison* OR teratogen* OR mutagen* OR carcinogen* OR genotox* OR neurotox* OR repro*) AND **TOPIC** (worker* OR workplace OR occupation*)

Scopus

TITLE-ABS-KEY ({BaMnO4} OR {KMnO4} OR {FeMn} OR {Mn2O3} OR {Mn3O4} OR {Mn3O7} OR{ Mn5O8} OR {Mn(NO3)2} OR {Mn(SO4)2} OR {Mn2(SO4)3} OR {MnCl2} OR {MnO} OR {MnO2} OR {MnSO4} OR {Na3MnO4} OR {SiMn} OR siliconmanganese OR {manganous salt} OR {manganous salts} OR braunite OR cianciulliite OR hausmannite OR polianite OR pyrochroite OR pyrolusite OR ramsdellite) AND TITLE-ABS-KEY (toxic* OR exposure* OR manganism OR parkinson* OR poison* OR teratogen* OR mutagen* OR carcinogen* OR genotox* OR neurotox* OR repro*) AND TITLE-ABS-KEY (worker* OR workplace OR occupation*)