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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 German 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-h 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.

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;

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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

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-h TWA or 15 min 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

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.

2.2.1. 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 h**, for a **40-h working** week and for a **working lifetime** (8-h TWA[4] OEL) and expressed as ppm or mg/m^3.

For some threshold chemicals, compliance with an 8-h 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-h 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.

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.

2.2.2. 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 and 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.

[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.

[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).