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# Derivation of an occupational exposure level for manganese in welding fumes

Lisa A. Bailey*, Laura E. Kerper, Julie E. Goodman

*Gradient, 20 University Road, Cambridge, MA 02138 USA*

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ABSTRACT

Exposure to high levels of manganese (Mn) in occupational settings is known to lead to adverse neurological effects. Since Mn is an essential nutrient, there are mechanisms that maintain its homeostatic control in the body, and there is some level of Mn in air that does not perturb Mn homeostasis. However, the Mn exposure concentrations at which no adverse effects are expected in occupational settings vary considerably across regulatory agencies. We set out to derive a Mn Occupational Exposure Level (OEL) for welders based on a review of studies that evaluated Mn exposure concentrations from welding fumes and: (1) neurological effects in welders; (2) levels of Mn in the brains of welders (*via* pallidal index [PI] estimated from magnetic resonance imaging [MRI]); (3) other biomarkers of Mn exposure in welders (*i.e.*, blood and urine); and (4) Mn brain concentrations, PI, and corresponding neurological effects in non-human primates. Our analysis suggests uncertainty in quantifying dose-response associations for Mn from many of the occupational welding studies. The few welding studies that adequately estimate exposure suggest a possible OEL of 100–140 $\mu g/m^3$ for respirable Mn. This range is consistent with other epidemiology studies, studies of biomarkers of Mn exposure in welders, and with studies in non-human primates, though future studies could provide a stronger basis for deriving a Mn occupational guideline for welders.



## 1. Introduction

Exposures to high levels of Mn in non-welding occupations (such as smelting, mining, or in the production or use of Mn alloys) have been shown to cause adverse neurological effects. Occupational guidelines for Mn reflect a wide range of concentrations (Table 1).

As reviewed by Bailey et al. (2009), several non-welding Mn occupational studies (*e.g.*, Gibbs et al., 1999; Deschamps et al., 2001; Young et al., 2005) are associated with a respirable ($PM_{2.5}$–$PM_{10}$) Mn No Observed Adverse Effect Level (NOAEL) for neurological effects of approximately 60 $\mu g/m^3$. This NOAEL is close to the 95% lower confidence limit associated with benchmark concentrations (BMCL) derived by the Agency for Toxic Substances and Disease Registry (Agency for Toxic Substances and Disease Registry (ATSDR), 2012) ($BMCL_{10}$ = 142 $\mu g/m^3$), California's Office of Environmental Health Hazard Assessment (CalOEHHA), 2008) ($BMCL_{05}$ = 72 $\mu g/m^3$), and Clewell et al. (2003) ($BMCL_{10}$ = 200 $\mu g/m^3$). Overall, since $BMCL_{10}$ values are recommended by US EPA as points of departure for derivation of toxicity values (US EPA, 2000, 2012), these studies suggest that an occupational Mn exposure level of 142–200 $\mu g/m^3$ (particulate Mn $PM_{2.5}$-$PM_{10}$) should be health protective for non-welding Mn occupations. These values are consistent with the former American Conference of Governmental Industrial Hygienists' (ACGIH) 8-h time-weighted average threshold limit value (TLV-TWA) for respirable particulate Mn of 200 $\mu g/m^3$. The ACGIH respirable Mn TLV, however, was recently revised to 20 $\mu g/m^3$ (American Conference of Governmental Industrial Hygienists (ACGIH), 2013).

Respirable Mn particles from non-welding occupational exposures (*e.g.*, smelting, mining, or in the production or use of Mn alloys) are generally >1.0 $\mu m$. During welding, Mn becomes airborne as an inhalable fume consisting of very small particles (<200 nm), potentially leading to higher absorption in the lungs (Flynn and Susi, 2009). Some animal studies suggest that very small inhaled Mn particles (<200 nm) can be transported from the nose directly to the brain *via* transport along the olfactory nerve (Dorman et al., 2006; Flynn and Susi, 2009; Elder et al., 2006). Consequently, it is reasonable to consider that Mn in welding

* Corresponding author.
*E-mail address:* lbailey@gradientcorp.com (L.A. Bailey).

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**Table 1**
Occupational Guidelines for Mn and Mn NOAEL and BMCLs from Occupational Studies of Mining, Smelting, or Alloy Production.

| Agency Value ($\mu$g/m$^3$) | | NOAEL ($\mu$g/m$^3$) | BMCL ($\mu$g/m$^3$) | Source(s) |
|---|---|---|---|---|
| NIOSH IDLH | 500,000 | – | – | US EPA Technology Transfer Network for Mn (US EPA, 2015) |
| OSHA ceiling | 5000 | – | – | |
| NIOSH REL | 1000 | – | – | |
| ACGIH TLV (inhalable) | 100 | – | – | American Conference of Governmental Industrial Hygienists (ACGIH), 2013 Inhalable = PM mass median aerodynamic diameter (MMAD) mostly >4 $\mu$m |
| ACGIH TLV (respirable) | 20 | – | – | American Conference of Governmental Industrial Hygienists (ACGIH), 2013 Respirable = PM MMAD mostly <4 $\mu$m. |
| – | – | 60[a] | – | Gibbs et al. (1999), Deschamps et al. (2001), and Young et al. (2005) |
| – | – | – | 200[a,b] | Roels et al. (1992) and Gibbs et al. (1999), as cited in Clewell et al. (2003) |
| – | – | – | 72[a,c] | California Office of Environmental Health Hazard Assessment (CalOEHHA) (2008) |
| – | – | – | 142[a,b] | Agency for Toxic Substances and Disease Registry (ATSDR), 2012 |

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BMCL = Benchmark Concentration Associated with a 95% Lower Confidence Limit; CalOEHHA = California Office of Environmental Health Hazard Assessment; IDLH = Immediately Dangerous to Life or Health; MMAD = Mass Median Aerodynamic Diameter; NIOSH=National Institute for Occupational Safety and Health; NOAEL = No Observed Adverse Effect Level; OSHA = Occupational Safety and Health Administration; PM = particulate matter; REL = Recommended Exposure Limit; TLV = Threshold Limit Value.

[a] Values are respirable ($PM_{2.5}$–$PM_{10}$).
[b] $BMCL_{10}$ (10% extra risk).
[c] $BMCL_{05}$ (5% extra risk).

fumes may enter the brain at higher rates than Mn particles from other types of exposure.

Here we review the scientific literature related specifically to associations between exposure to Mn in welding fumes and neurological effects, and propose a Mn Occupational Exposure Level (OEL) for welders that is supported by the current science. Because our analysis is based on only a few well-conducted studies, we describe additional studies that will provide a stronger basis for deriving Mn occupational guidelines for welders and other occupations.

## 2. Methods

We conducted a literature search in PubMed (through October 2016) for studies that evaluated exposure-response relationships between inhalation concentrations of Mn in welding fumes and subclinical neurological effects. We used the following search terms: "((welders OR welding) AND (manganese OR "Mn") AND (neuropsych* OR neurocognitive OR neurolog* OR neurotoxic* OR neurobehav* OR cognitive OR memory OR motor OR mood OR speech)) OR ((monkey OR primate) AND (weld* OR welding) AND (manganese OR "Mn") AND (neurolog* OR neurotoxic* OR neurobehav* OR motor))." We identified 155 studies with these search terms.

To capture additional studies that evaluated relationships between Mn inhalation exposure concentrations from welding fumes and biomarkers of Mn exposure, we conducted an additional literature search in PubMed (through October 2016) with the following search terms: "((welders OR welding) AND (manganese OR "Mn") AND (biomarker) AND (blood OR plasma OR urine OR brain))" and excluded all studies that were captured in our original search. We identified 28 additional studies with this search strategy.

From these 183 studies, we identified studies that met two sets of criteria, which are summarized in Table 2. Case reports were not included.

We also reviewed the references cited within our selected studies to identify review articles, *meta*-analyses, and other supporting articles relevant to our analysis.

Based on our critical review of the welding epidemiology and animal studies and a determination of Mn dose-response relationships for neurological effects, we estimated a Mn OEL that is health-protective for welders.

**Table 2**
Summary of Study Selection.

| Neurological Effect Studies | Biomarker Studies (No Neurological Effects) |
|---|---|
| Criteria:<br>• Evaluated welding exposures as separate exposure group;<br>• Measured Mn inhalation exposure concentrations; and<br>• Measured neurological effects. | Criteria:<br>• Evaluated welding exposures as separate exposure group;<br>• Measured Mn inhalation exposure concentrations;<br>• Measured biomarkers of Mn exposure (blood, plasma, or urine), conducted magnetic resonance imaging (MRI), or a combination; and<br>• Did not evaluate neurological effects. |
| Studies that met the criteria:<br>• 22 occupational studies were selected, and 2 additional studies were identified within a review article.<br>• 1 primate study was identified. | Studies that met the criteria:<br>• 8 occupational studies were selected, and 1 additional study was identified within the selected studies.<br>• 1 primate study was identified. |
| Total welder studies = 24<br>Total primate studies = 1 | Total welder studies = 9<br>Total primate studies = 1 |

Mn = Manganese.