Review of Scientific Evidence Related to Potential Toxicity of Occupational Exposure to Airborne Manganese, Prepared for Consideration by the California Division of Occupational Safety and Health (DOSH)

Prepared for
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GRADIENT

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygiene
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMD_{10}	Benchmark Dose for a 10% Increase in Risk
BMDL	95% Lower Confidence Limit on the Benchmark Dose
$BMDL_{05}$	95% Lower Confidence Limit on the Benchmark Dose Associated with a 5% Increase in Risk
$BMDL_{10}$	95% Lower Confidence Limit on the Benchmark Dose Associated with a 10% Increase in Risk
CalOEHHA	California Office of Environmental Health Hazard Assessment
CPT	Continuous Performance Test
DOSH	California Division of Occupational Safety and Health
GABA	Gamma-amminobutyric Acid
Geomean	Geometric Mean
MMAW	Manual Metal Arc Welding
Mn	Manganese
MRI	Magnetic Resonance Imaging
MRL	Minimal Risk Level
MRS	Magnetic Resonance Spectroscopy
NOAEL	No Observed Adverse Effect Level
NRC	National Research Council
OEL	Occupational Exposure Limit
PBPK	Physiologically Based Pharmacokinetic
PEL	Permissible Exposure Limit
POD	Point of Departure
R1	Longitudinal Relaxation Rate
REL	Reference Exposure Level
SD	Standard Deviation
TLV	Threshold Limit Value
TWA	Time-weighted Average
UF	Uncertainty Factor
US EPA	United States Environmental Protection Agency

1   Introduction

This report summarizes the results reported in Bailey *et al.* (2017) regarding a proposed Occupational Exposure Limit (OEL) for manganese (Mn) in welding fumes, and provides an update to that study based on several more recent studies of neurological effect in welders. In addition, we provide suggestions for how to interpret the welder neurological effect studies, considering the variability within the Mn exposure concentrations reported in those studies. Based on our analysis, we provide a review of the proposed California Division of Occupational Safety and Health (referred to as "DOSH" throughout) Mn Permissible Exposure Limit (PEL) of 20 μg/m^3 for welding fumes (DOSH, 2018) and suggest revisions to that value. We suggest that the analysis and conclusions of this report be presented to DOSH for its consideration as it determines the adequacy of the current PEL for airborne exposure to Mn.

2 Background on Manganese Toxicity and Essentiality

2.1 Introduction to Toxicology

An understanding of the scientific principles in the fields of toxicology and risk assessment is necessary for evaluating the potential for a causal relationship between exposure to chemicals and health effects. One of the most fundamental concepts in the field of toxicology is the dose-response relationship. This concept is commonly summarized as "the dose makes the poison" (Eaton and Gilbert, 2013). All substances exhibit a dose-response relationship, with an increasing level of response observed with increasing doses. However, for most chemicals, biological effects occur only when the dose exceeds a threshold level for a certain period of time. At doses ranging between zero and the threshold, biochemical or physiological mechanisms can negate a chemical's effects, thereby preventing any potential adverse effects. As the magnitude and duration of exposure begin to exceed the threshold, these protective mechanisms can become less effective. Consequently, the effect begins to appear in a manner that corresponds to the increase in dose.

Although virtually all substances can produce toxic effects at some dose, the range of doses necessary to produce an adverse effect varies widely by substance. Not all biological and physiological changes that occur in response to an exposure are adverse. In fact, some substances are beneficial at low doses. For example, small amounts of salt may be consumed without adverse effects, because the body requires some level of salt intake and is able to adequately maintain proper salinity levels in its fluids and tissues. The adequate intake of salt needed to sustain health ranges from 3-3.8 grams per day, depending on age, gender, and lifestyle (active or sedentary) (IOM, 2005). However, ingestion of much larger quantities of salt can override these homeostatic mechanisms and cause adverse effects, such as hypertension, in some individuals (IOM, 2005). Another example is essential metals. Small amounts of essential metals (such as Mn) are necessary to maintain normal biological function in living organisms, but at much higher doses, essential metals can cause adverse effects.

The National Research Council (NRC) has described a continuum of biological effects that occur after an exposure to a particular substance (NRC, 2007). Exposure to a small amount of a substance may cause an adaptive response, allowing the organism to maintain normal functionality (*i.e.*, homeostasis). If the exposure is sufficiently large, homeostatic mechanisms may be overwhelmed, which can then lead to cell injury and adverse health effects. There are many types of physiological changes that fall along the continuum from beneficial to adverse effects, a number of which are not considered adverse. Distinguishing non-adverse from adverse effects is critical for determining at what dose or concentration an exposure can cause adverse effects. See a recent review article by Goodman *et al*. (2010) that describes this continuum and a framework for assessing causality and adverse effects in humans.

2.2 Manganese Essentiality and Toxicity

Mn is a naturally occurring element and the fifth-most-abundant metal in the Earth's crust. Mn is an essential nutrient that is necessary for the function of several enzyme systems and cell energy production in humans. A sufficient intake of Mn is needed for the formation of healthy cartilage and bone (ATSDR, 2012) and for neuronal health (Horning *et al*., 2015; Chen *et al*., 2015). Therefore, a deficiency of Mn can cause adverse health effects, including adverse neurological effects. In addition, once Mn exposure (*via*

ingestion or inhalation) exceeds levels that can be managed by homeostatic mechanisms, excess Mn can accumulate in the brain and can lead to adverse neurological effects (ATSDR, 2012; Horning *et al*., 2015). Therefore, maintaining appropriate levels of Mn in the body is critical for human health.

The fact that Mn is an essential nutrient and not simply a toxic agent, *e.g*., lead or arsenic, puts the determination of appropriate exposure limits in a category distinct from many other occupational toxicants. Perhaps most importantly, the fact that it is a nutrient and is present in detectable amounts that can be considered desirable and healthy in human tissues presents an opportunity to collect data on exposure toxicity that do not exist for other potentially harmful chemical agents in the work environment.

The most common health effects associated with chronic inhalation of elevated levels of Mn in occupational environments are neuromotor deficits (*e.g*., tremor, hand-eye coordination) (ATSDR, 2012). It is currently known with scientific certainty that chronic exposure to high levels of Mn in air (*i.e*., greater than 2,000 µg/m^3) can cause a disabling syndrome called "manganism," the symptoms of which include a dull affect, altered gait, fine tremor, headaches, and sometimes psychiatric disturbances (ATSDR, 2012). Studies of occupational exposure to lower levels of Mn in air have reported some subclinical (subtle) neurological effects. These studies have been used to estimate levels of Mn in air that lead to no adverse neurological effects (*i.e*., no subclinical effects). These studies are described in more detail in Section 4.

There are several studies that also provide information on Mn levels in air above which levels of Mn in the body begin to increase (*e.g*., Schroeter *et al*., 2011). Importantly, many of these studies do not evaluate adverse effects. It is important to consider these studies as informing relationships between measurements of Mn in air and biomarkers of Mn exposure, and not as markers of adverse effect. Neurological effect studies are needed to address associations between Mn levels in air and adverse effects. As described by Goodman *et al*. (2010), although some adaptive responses may overwhelm homeostatic mechanisms at higher doses (such as changes in Mn levels in the brain at higher Mn exposures), at lower levels of exposure, these responses (such as small changes in Mn levels in the brain) are not adverse if they are considered early precursor effects, reversible, of low severity, or do not result in functional impairment. It is also important to consider that because Mn is an essential nutrient, there is a range of levels of Mn in the brain that is considered normal (see further discussion below), and a change that is within the normal range will not result in functional impairment.

Therefore, to understand what levels of Mn in air may lead to (or not lead to) adverse effects, it is critical to consider studies that evaluate associations between levels of Mn in air and adverse effects, in addition to studies of biomarkers of exposure. Studies that only evaluate associations between levels of Mn in air and changes in Mn levels in the brain are useful for informing no effect levels, but cannot, by themselves, inform effect levels.

2.2.1   Range of Normal Levels of Mn in the Human Brain

Schroeter *et al*. (2011) describe the development of a human Mn physiologically based pharmacokinetic (PBPK) model that predicts human Mn tissue concentrations that are associated with different Mn respirable inhalation concentrations. As described by Schroeter *et al*. (2011):

> At the lowest exposure concentration (0.01 mg/m^3 Mn), the model predicted no appreciable increase (< 1%) in brain Mn concentrations above background levels that result from normal dietary exposure. At an exposure concentration of 0.1 mg/m^3, slight increases (~5%) in brain Mn concentration above background levels were observed during the inhalation exposure period. More significant (> 30%) increases in brain Mn concentrations were predicted at the higher exposure concentrations (> 1.0 mg/m^3).

Therefore, the Mn PBPK model predicts only a slight increase in Mn levels in the brain at 100 $\mu g/m^3$ (0.1 mg/m^3) respirable Mn. As described above, this slight increase does not mean that 100 $\mu g/m^3$ Mn in air will cause neurological effects. As described by Schroeter *et al*. (2011) and Ramoju *et al*. (2017), normal levels of Mn in the human globus pallidus (*i.e*., the area of the brain that is the presumed target for neuromotor effects from Mn exposure) range from approximately 0.24-0.64 $\mu g/g$ (based on autopsy results from healthy subjects), with 0.64 $\mu g/g$ correlating approximately with an occupational inhalation exposure concentration of 140 $\mu g/m^3$ respirable Mn. A respirable Mn concentration of 142 $\mu g/m^3$ was the point of departure (POD) (considered approximately equivalent to a no observed adverse effect level [NOAEL]) applied by the Agency for Toxic Substances and Disease Registry (ATSDR) in derivation of its Minimal Risk Level (MRL) for Mn (ATSDR, 2012) for general population risk assessment (described in more detail in the next section). The ATSDR POD is based on a neurological effect study of battery facility workers occupationally exposed to Mn (Roels *et al*., 1992).

Therefore, the most current scientific evidence for Mn levels in the brain and adverse effects suggests that slight increases in Mn brain concentrations at 100 $\mu g/m^3$ respirable Mn are within the range of normal and can increase up to at least 140 $\mu g/m^3$ without significantly impacting levels in the brain and without leading to functional impairment. It is important to consider that 140 $\mu g/m^3$ is not a bright line above which effects will occur. Small increases in Mn brain concentrations that may occur at Mn inhalation concentrations slightly higher than 140 $\mu g/m^3$ may also not lead to functional impairment. As noted by Schroeter *et al*. (2011), it is not until around 1,000 mg/m^3 Mn in air that more significant increases (*i.e*., "> 30%") in brain concentrations are predicted.

Section 4 describes occupational neurological effect studies of Mn in welding fumes and proposes a NOAEL based on those studies. The results provide support that exposure to 140 $\mu g/m^3$ respirable Mn in welding fumes and possibly higher (200 $\mu g/m^3$) are not likely to impact normal levels of Mn in the brain and would not be expected to lead to adverse health effects; the welding study results are similar to non-welding Mn occupational studies (*i.e*., 142 $\mu g/m^3$ POD from the Roels *et al*. [1992] battery facility worker study).

3   Occupational No Effect Levels and Exposure Limits for Respirable Mn

The most recent published OEL for respirable Mn available in the United States is the American Conference of Governmental Industrial Hygiene (ACGIH) Threshold Limit Value (TLV) of 20 μg/m^3, published in 2013 (ACGIH, 2013). The 20 μg/m^3 value is based on the Roels *et al*. (1992) study of battery facility workers occupationally exposed to respirable Mn in air. However, the methodology applied by ACGIH to derive the TLV is not statistically robust and is not consistent with the current standard of risk assessment practice. ACGIH used the regression function from the Roels *et al*. (1992) study to determine the respirable Mn concentrations corresponding to a 5%, 2.5%, and 1% greater probability of developing abnormal hand steadiness compared to controls. They chose a value of 20 μg/m^3 as the TLV for respirable Mn, corresponding to a 2.5% greater probability of abnormal effects compared to controls from the Roels *et al*. (1992) regression model. The United States Environmental Protection Agency (US EPA) recommends applying its benchmark dose (BMD) software (US EPA, 2000, 2012) to derive toxicity reference criteria. Therefore, BMD modeling of the Roels *et al*. (1992) or other Mn occupational data is the more appropriate approach for deriving a Mn occupational toxicity reference value (such as a TLV).

ATSDR recently applied US EPA's BMD software to the Roels *et al*. (1992) data to derive an Mn POD of 142 μg/m^3 for respirable Mn for derivation of its MRL. The 142 μg/m^3 value is equivalent to a BMDL$_{10}$ (95% lower confidence limit on the BMD associated with a 10% increase in risk). US EPA recommends applying a BMDL$_{10}$ for a POD, because this value corresponds approximately to a NOAEL (US EPA, 2000, 2012). Therefore, had ACGIH applied the most current scientific methodology (BMD modeling) to derive a no effect level from the Roels *et al*. (1992) data, it would have derived a respirable Mn TLV closer to 142 μg/m^3 based on a BMDL$_{10}$.

The California Office of Environmental Health Hazard Assessment (CalOEHHA) derived a BMDL$_{05}$ (95% lower confidence limit on the BMD associated with a 5% increase in risk) of 72 μg/m^3 from the same data set (Roels *et al*., 1992) as a POD for deriving its Mn chronic Reference Exposure Level (REL) for general population risk assessment (CalOEHHA, 2008). The 142 μg/m^3 and 72 μg/m^3 values are 3.5- to 7-fold higher, respectively, than the 20 μg/m^3 Mn TLV. As discussed in Section 2, occupational exposure to both of these respirable Mn concentrations (72 and 142 μg/m^3) are not expected to impact normal levels of Mn in the brain.

Table 3.1 summarizes the derivation of the ACGIH respirable Mn TLV and the ATSDR and CalOEHHA respirable Mn PODs. Also summarized, for comparison, is the recently proposed DOSH respirable Mn PEL (DOSH, 2018).

Table 3.1 Mn Respirable OELs and No Effect Levels from Occupational Studies

Parameter	ACGIH TLV (2012)	ATSDR MRL POD (2012)	CalOEHHA REL POD (2008)	DOSH Proposed PEL (2018)
Key study	Roels *et al.* (1992) (study of battery facility workers)			
Value	20 µg/m^3	142 µg/m^3	72 µg/m^3	20 µg/m^3
Methodology for derivation of a no effect level	Regression equation from Roels *et al.* (1992) for 2.5% increased risk	BMDL$_{10}$	BMDL$_{05}$	BMDL$_{05}$ of 77 µg/m^3 ÷ UF of 3 ("due to the greater potential for pulmonary deposition/absorption of Mn fume")
Comment on methodology	Not a scientifically robust calculation	Best methodology (US EPA-recommended)	US EPA methodology (CalOEHHA application of BMDL$_{05}$)	The best available science suggests no UF is needed for increased bioavailability of Mn in welding fume
Mn level in the brain (globus pallidus)	All concentrations predicted to result in normal levels of Mn in the brain (Schroeter *et al.*, 2011; Ramoju *et al.*, 2017)			

Notes:
ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BMDL$_{05}$ = 95% lower Confidence Limit on the Benchmark Dose Associated with a 5% Increase in Risk; BMDL$_{10}$= 95% Lower Confidence Limit on the Benchmark Dose Associated with a 10% Increase in Risk; CalOEHHA = California Office of Environmental Health Hazard Assessment; DOSH = California Division of Occupational Safety and Health; Mn = Manganese; MRL = Minimal Risk Level; OEL = Occupational Exposure Limit; PEL = Permissible Exposure Limit; POD = Point of Departure; REL = Reference Exposure Level; TLV = Threshold Limit Value; UF = Uncertainty Factory; US EPA = United States Environmental Protection Agency.

As shown in Table 3.1, 142 µg/m^3 reflects the best methodology, recommended by US EPA, for a no effect level for occupational exposure to respirable Mn. The other, lower values (20-72 µg/m^3) are based on a less scientifically robust methodology (ACGIH TLV) or a 5% increased risk instead of a 10% increased risk (CalOEHHA and DOSH) that provides no added benefit, because both the 5% and 10% risks reflect exposure concentrations that are not expected to impact normal levels of Mn in the brain. The DOSH proposed PEL also includes an uncertainty factor (UF) of 3 for increased bioavailability of Mn in welding fume, which, as discussed in Sections 3.1 and 4, is unnecessary, as indicated by welder neurological effect studies that support a no effect level of 140 µg/m^3 (or possibly higher) for Mn in welding fumes.

3.1 A UF of 3 for Greater Potential for Pulmonary Deposition or Absorption of Mn in Fume Is Unnecessary

The proposed DOSH Mn PEL includes a UF of 3 applied to an Mn respirable BMDL$_{05}$ of 77 µg/m^3 to derive a PEL of 20 µg/m^3 for Mn fumes based on "greater potential for pulmonary deposition/absorption of Mn fume" (DOSH, 2018). UFs are typically applied during toxicity criteria derivation only when there is inadequate scientific information available to address the uncertainty. However, as discussed below, the most current scientific information available suggests a UF of 3 for increased bioavailability of Mn in welding fume is unnecessary.

Because the Roels *et al.* (1992) study is a battery facility worker study, and not a welder study, and welding fume particles are smaller in diameter than the Mn particles in air that may be present for battery workers or smelter workers, it is reasonable to consider whether Mn particles in welding fumes may be absorbed more readily in the body (*i.e.*, may be more bioavailable) than those in the battery worker study. However, the DOSH Mn PEL summary document (DOSH, 2018) does not provide a discussion of the studies that it

reviewed to support an assumption of increased bioavailability of Mn in fumes. Further, we are not aware of any studies that suggest that Mn particles in welding fumes are more bioavailable (*i.e.*, deposit more readily in the respiratory tract, or are more readily transported to the brain [globus pallidus]) than larger respirable Mn particles. In addition, as discussed in Section 2, exposure studies (such as a bioavailability study) inform exposure estimates and not effect levels. Effect studies are more appropriate, if available, for addressing whether potential increased bioavailability may lead to an increased risk of adverse effects, and at what exposure concentration.

In the case of Mn in welding fumes, as discussed in Section 4 and in a recent study by Bailey *et al.* (2017), the welding neurological effect studies suggest a NOAEL for Mn in welding fumes of 140 $\mu g/m^3$ (or possibly as high as 200 $\mu g/m^3$), the same as the most scientifically supported no effect level for Mn from the Roels *et al.* (1992) battery worker study (142 $\mu g/m^3$).

Therefore, the most current scientific information suggests that Mn particles in welding fumes are not more bioavailable and do not result in an increased risk for neurological effects compared to Mn respirable particles in other occupations, such as battery workers or smelter workers. Consequently, a UF of 3 for increased bioavailability of Mn in fumes, as was applied by DOSH, is not necessary.

4 Welder Neurological Effect Studies

As described in a recent article by Bailey *et al.* (2017), in which the authors reviewed 24 neurological effect studies of welders and 9 welder studies that evaluated biomarkers of Mn exposure, the current available scientific information provides support for an OEL of 140 μg/m^3 for Mn in welding fumes. Several studies published after Bailey *et al.* (2017) provide additional support for a Mn OEL of 140 μg/m^3 (and possibly higher) (van Thriel *et al.*, 2017; Ma *et al.*, 2018). These studies are described below, in addition to further discussion of the main dose-response studies that were described in Bailey *et al.* (2017): Ellingsen *et al.* (2008) and Park *et al.* (2009).

In this section, we also review the only two welding studies (Bowler *et al.*, 2007; Laohaudomchok *et al.*, 2011) that are discussed by DOSH in its Mn PEL summary document (DOSH, 2018).

4.1 San Francisco Bay Bridge Welder Studies (Bowler *et al.*, 2007; Park *et al.*, 2009)

Bowler *et al.* (2007) conducted a study of 43 confined-space welders involved in the construction of the San Francisco-Oakland Bay Bridge. Personal air monitoring data showed work shift mean time-weighted average (TWA) Mn concentrations ranging from 110-460 μg/m^3, with a mean of 210 μg/m^3. The authors reported cognitive/memory effects and fine motor deficits in approximately 60% of the welders. However, the authors also noted that 55% of the workers were exposed to concentrations above 200 μg/m^3; therefore, it is conceivable that workers exposed to Mn levels higher than 200 μg/m^3 may have largely influenced the neurological effect test results. Park *et al.* (2009) conducted a re-analysis of the same data, applying US EPA's BMD software (US EPA, 2000, 2012) to derive Mn BMDL values for neurological effects. The authors observed dose-response correlations between five of eight cognitive test scores and cumulative Mn exposure, and calculated BMDs for a 10% increase in risk (BMD$_{10}$) ranging from 72-104 μg/m^3 for these cognitive tests.

These studies require careful interpretation, because there was no control group (*i.e.*, scores were compared to "the test publishers' norms" [Bowler *et al.*, 2007]), the study group was small, and the results are potentially biased, because the subjects were involved in worker's compensation evaluations. In addition, the studied welders had already welded for 14.2 years on average before welding on the Bay Bridge construction project, which took place for only 1.5 years. Therefore, it is not possible to determine the impact of from the welders' past welding experience on their neurological test results. Mn exposures from the welders' previous welding experiences are unknown and could have been higher than those reported during the welding work done for the Bay Bridge.

Despite the uncertainties and possible bias in these studies, the Mn BMD$_{10}$ values of 72-104 μg/m^3 are still well above the current ACGIH Mn TLV of 20 μg/m^3.

4.2 Laohaudomchok *et al.* (2011)

A study by Laohaudomchok *et al.* (2011) reported subclinical symptoms in welders, with a median respirable Mn exposure of 12.9 μg/m^3. The authors reported correlations between cumulative exposure for the past 12 months and mood disturbances for 3 of 10 mood states (sad, tense, and confused). They also

reported correlations between cumulative total exposure and mean reaction time (one of five performance tests) and between cumulative total exposure and disturbances in three mood states (confused, tired, and a composite of tired/energetic), two of which were different from the 12-month exposure correlations. The results of this study must be interpreted with caution, however, because there was no control group used for comparison, the mood associations lacked consistency across exposure measures, and some of the mood associations ceased to be significant when the three welders with the highest cumulative exposure indices (>100 mg/m^3-hour) were excluded. Thus, if there is an association between exposure and mood disturbance, the data suggest that it would be more likely to occur at concentrations greater than 90 μg/m^3 (assuming approximately 1,118 hours of welding time, as described in the study) although the highly exposed study group was too small to make this conclusion with any certainty. In addition, the exposure estimates in this study are uncertain because samples were collected from a monitor on the welder's shoulder and not under the mask, within the breathing zone.

The authors made the following statements with respect to the study results and possible influence of a few higher-exposed welders:

> When three participants with total work history Mn-CEI higher than 100 mg/m^3-hr were excluded, the association was similar for the CPT [continuous performance test] scores (β=0.67, p=0.04). However, the associations with POMS confusion and tiredness scales were no longer significant (β=0.02, p=0.77 and β=0.14, p=0.52, respectively).

> As can be seen, the significant associations [CPT and handwriting stability test] were largely dependent on one welder with the highest exposure over the day.

It is noteworthy that once the three higher-exposed individuals were excluded, the *p* value for the continuous performance test (CPT) score went from significant (*p* < 0.01) to a *p* value of 0.04, which is only borderline significant. Therefore, the exposure-response relationship is most likely due to the higher exposed welders. Consequently, a quantitative dose-response relationship cannot be established from this study.

4.3   Ellingsen *et al*. (2008)

Ellingsen *et al*. (2008) evaluated neuromotor and cognitive effects in 96 welders and 96 matched controls (cross-sectional study), and examined low (geometric mean [geomean]: 31 μg/m^3, range: 7-88 μg/m^3), medium (geomean: 137 μg/m^3, range: 88-198 μg/m^3), and high (geomean: 423 μg/m^3, range: 204-2,322 μg/m^3) Mn exposure concentrations (measured *via* personal air monitors under the helmet). The authors observed subclinical neurological effects in the medium and high, but not the low, exposure groups, and only the high exposure group was statistically significantly different from the control group, suggesting an Mn NOAEL of 137 μg/m^3 based on a mean Mn concentration in welding fumes.

4.4   van Thriel *et al*. (2017)

van Thriel *et al*. (2017) evaluated multitasking and cognitive flexibility in 47 welders and 26 age-matched controls (cross-sectional study), and examined a low Mn exposure group (21 welders, median: 4.7 μg/m^3, Q1 = 2.3 μg/m^3, Q3 = 9.28 μg/m^3) and a high Mn exposed group (26 welders, median: 92.5 μg/m^3, Q1 = 41 μg/m^3, Q3 = 150 μg/m^3)[1] (measured *via* personal air monitors under the helmet). The authors found no differences in multitasking performance or cognitive flexibility between the welders and controls for both the low and high Mn exposure groups. The authors reported a weak association between education level

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[1] Q1 = 25th percentile; Q3 = 75th percentile.

and cognitive flexibility and noted that controls were not matched for education level. The results of this study suggest a NOEAL of 93 μg/m³ based on a median Mn concentration in welding fumes.

4.5 Ma *et al.* (2018)

Ma *et al.* (2018) evaluated neuromotor effects in 39 welders and 22 age-matched controls (cross-sectional study), and examined a low Mn exposure group (26 welders, mean: 130 μg/m³ ± 100 standard deviation [SD]) and a high Mn exposure group (13 welders, mean: 230 ± 180 μg/m³ SD) (measured *via* personal air monitors under the helmet). The authors found a significant increase in neuromotor effects in the high exposure group compared to controls but found no increase in effects in the low exposure group compared to controls.

Ma *et al.* (2018) also used non-invasive MEGA-edited magnetic resonance spectroscopy (MRS) to evaluate changes in gamma-amminobutyric acid (GABA), a thalamic neurometabolite in brain. GABA is known to play a key role in mediating neuronal pathways in the basal ganglia, which has been shown to be a primary target for Mn (*i.e.*, the globus pallidus within the basal ganglia) (Ma *et al.*, 2018). The authors observed a significant increase in GABA levels in the brain in the higher exposure group compared to controls. GABA levels in the lower exposure group, however, were not different from controls. The authors concluded that "GABA levels and motor function displayed a non-linear pattern of response to Mn exposure, suggesting a threshold effect" (Ma *et al.*, 2018).

The authors also conducted magnetic resonance imaging (MRI) to evaluate Mn deposition in the brain *via* longitudinal relaxation rate (R1) changes. The authors observed an association between R1 and Mn exposure in both the low exposure group (mean Mn: 130 μg/m³) and high exposure group (mean Mn: 230 μg/m³). These results are consistent with changes in the levels of Mn in the brain at exposure concentrations lower than those at which adverse effects are observed. That is, the difference in Mn levels in the brain in the lower exposure group (compared to controls) can be interpreted to be within the normal range and, therefore, reflects a biomarker of low-level Mn exposure that is not associate with adverse effects.

This is the first study to evaluate associations between Mn levels in air (for at least two different exposure groups) and neurological effects in welders, in addition to evaluating levels of Mn in brain and levels of a biomarker of neurological effect in the brain (GABA). The results of this study suggest a NOAEL of 130 μg/m³ based on mean Mn concentration in welding fumes.

4.6 Conclusion

Based on the studies reviewed in our recent publication (Bailey *et al.*, 2017), and the two studies published since then (Ma *et al.*, 2017; van Thriel *et al.*, 2017), the welding studies that most adequately evaluate a dose-response relationship between Mn in welding fumes and neurological effects are Ellingsen *et al.* (2008), Ma *et al.* (2018), and van Thriel *et al.* (2017). Although Park *et al.* (2009) did conduct a more robust dose-response evaluation than Bowler *et al.* (2007), interpretation of the Bay Bridge welding study results is complicated due to the limited exposure duration of the subjects on the Bay Bridge project, limited knowledge of the subjects' prior welding exposures, other limitations in study design (*i.e.*, no control group), and potential bias because the subjects were involved in a workers' compensation case. Drawing quantitative conclusions regarding Mn exposure in welding fumes and adverse health effects from the Laohaudomchok *et al.* (2011) study is also limited, as discussed above, due to the possible influence of a few higher-exposed individuals.

The three welding studies described here that have the most reliable dose-response information applicable to the derivation of a no effect level for Mn in welding fumes (Ellingsen *et al*., 2008; Ma *et al*., 2018; van Thriel *et al*., 2017) suggest a health-protective NOAEL of approximately 140 μg/m^3, based on a range of means (or median) of approximately 93-137 μg/m^3. However, as discussed in the next section, it is important to consider that the mean and median concentrations for the NOAEL groups reflect a range of Mn concentrations, with the high end only slightly higher than 140 μg/m^3, close to 200 μg/m^3 for all three studies. Therefore, it is important to consider the exposure variability within that range and whether the upper end may also reflect an Mn concentration that is likely to be associated with no adverse neurological effects.

5 Interpretation of Current Welder Neurological Effect Studies and Implications for Derivation of an OEL for Mn in Welding Fumes

Figure 5.1 summarizes the results from the key Mn biomarker welding studies discussed in Bailey *et al.* (2017), in addition to the NOAEL results from three key neurological effect studies described in Section 4.
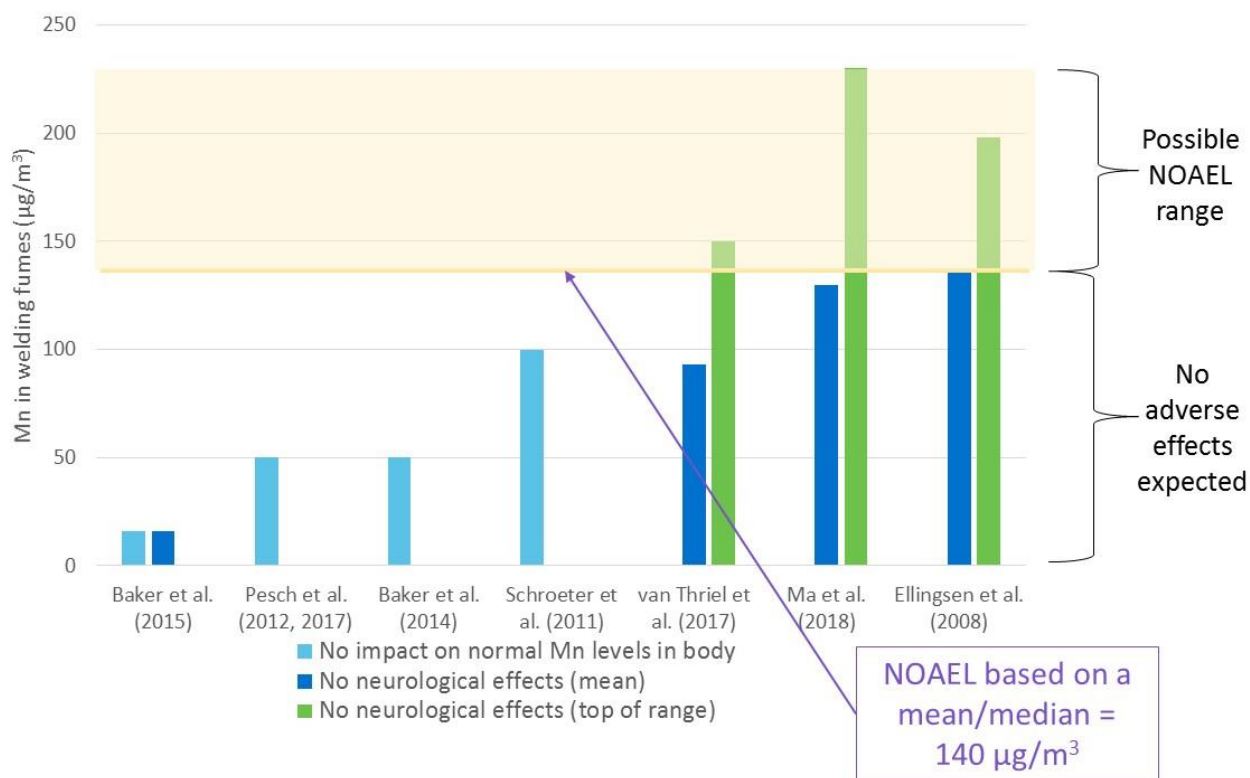

Figure 5.1 Summary of No Effect Levels for Mn in Welding Fumes. The shaded region reflects the upper end of the range above the mean or median from the three neurological effects studies, and is considered a possible upper end of the NOAEL range.

As shown in Figure 5.1, although the mean Mn concentrations from the studies suggest an Mn NOAEL of 140 $\mu g/m^3$, the upper end of the range for those values is close to 200 $\mu g/m^3$. In addition, the exposure concentration ranges for the two studies in which effects were observed include individual exposure levels that are much higher than 200 $\mu g/m^3$: mean of 423 $\mu g/m^3$ (range of 204-2,000 $\mu g/m^3$) for Ellingsen *et al.* (2008), and mean of 230 $\mu g/m^3$ (approximate range of 50-410 $\mu g/m^3$ within the SD) for Ma *et al.* (2018). van Thriel *et al.* (2017) did not report effects in any exposure group. Therefore, the precise Mn dose at which neurological effects begin and at which GABA levels begin to increase in the brain is unclear, and likely varies between individuals depending on dietary intake of Mn. Based on the means and ranges from these studies, one can predict that the effect level is likely higher than 140 or 200 $\mu g/m^3$, but could be as high or higher than 400 $\mu g/m^3$, because effects in the higher-exposed groups are likely driven more by

individuals exposed to the higher Mn concentrations (410-2,000 µg/m^3) than by individuals exposed to the lower Mn concentrations.

5.1 Consideration of the Mn PBPK Model to Estimate Levels of Mn in the Human Brain Following Inhalation of 200 µg/m^3 Mn

To try to better understand the potential differences in exposure to 140 µg/m^3 *vs*. 200 µg/m^3 Mn in welding fumes in terms of potential adverse effect, we used the results described in the Schroeter *et al*. (2011) PBPK model to derive a semi-quantitative estimate of Mn levels in the brain following exposure to 200 µg/m^3 Mn in welding fumes. As described in Section 2, at a Mn exposure concentration of 100 µg/m^3, the PBPK model predicts only slight increases (~5%) in brain Mn concentration above background levels. The model predicts more significant (>30%) increases in Mn brain concentrations at the higher exposure concentrations (>1,000 µg/m^3). If we assume a 10% increase in Mn brain concentration from inhalation of 200 µg/m^3 Mn from that associated with a Mn inhalation concentration of 140 µg/m^3 (0.64 µg/g), which can be considered a conservative estimate, because 200 µg/m^3 is still well below 1,000 µg/m^3, we estimate a Mn brain concentration of approximately 0.7 µg/g. The calculation is as follows: 0.64 µg/g + 0.064 = 0.70 µg/g.

The difference between 0.64 and 0.70 µg/g Mn in the brain seems fairly small, and one could suggest that this small increase is still within, or at least very close to, the normal range of Mn levels in the brain, particularly given that the top of the range of means for NOAELs from the three neurological effect studies described herein is approximately 200 µg/m^3 Mn.

5.2 Consideration of Non-human Primate Studies

To provide additional support for 0.7 µg/g as being a normal level of Mn in the human brain, one can consider two studies that examined non-human primate exposure to manual metal arc welding (MMAW) fumes, neurological effects, and Mn concentrations in the globus pallidus (Han *et al*., 2008; Kim *et al*., 2013). Han *et al*. (2008) examined brain concentrations in monkeys exposed to Mn in welding fumes at low (900 µg/m^3) and high (1,950 µg/m^3) concentrations (for 2 hours/day, 5 days/week, for 35 weeks) in a controlled laboratory setting. These concentrations are roughly comparable to an 8-hour TWA Mn concentration of 225 µg/m^3 and 490 µg/m^3, respectively (*e.g.*, 900 µg/m^3 × 2/8 hours/day = 225 µg/m^3). The authors observed Mn concentrations in the globus pallidus of approximately 1.2 µg/g and 1.4 µg/g at the low and high exposure concentrations, respectively, compared to a concentration of approximately 0.6 µg/g in the unexposed controls (similar to background Mn levels in the human brain). Another study from the same laboratory (Kim *et al*., 2013) examined locomotor changes in the same study group of monkeys. The authors found that locomotor effects in monkeys exposed to the lowest concentration (equivalent to 225 µg/m^3 8-hour TWA) were not different from the no exposure control group, suggesting a globus pallidus NOAEL of 1.2 µg/g Mn and a NOAEL for Mn in welding fumes of 225 µg/m^3 8-hour TWA.

Another study by Schroeter *et al*. (2012) applied the rhesus monkey PBPK model to evaluate a dose-response relationship between Mn brain concentrations and neurological effects. The authors simulated Mn exposure scenarios from 15 monkey studies, in which exposure and neurological effect data were available, to predict corresponding increases in Mn brain concentrations. Schroeter *et al*. (2012) predicted that a 10% increased risk of slight-to-mild neurological effects (motor effects) in monkeys would correspond to a globus pallidus Mn concentration of 0.8 µg/g. Because US EPA's BMD guidance document recommends that a 10% increased risk of a slight-to-mild adverse effect can be applied as a NOAEL (US EPA, 2000, 2012), we can use the Schroeter *et al*. (2012) results to suggest a Mn globus pallidus NOAEL of 0.8 µg/g.

Therefore, the non-human primate neurological effect studies suggest that Mn brain concentrations of 0.8-1.2 μg/g are unlikely to lead to adverse neurological effects. These results provide supporting evidence that a Mn level of 0.7 μg/g in the human brain (possibly associated with an Mn inhalation concentration of approximately 200 μg/m^3) would also not lead to adverse neurological effects.

5.3   Conclusion and Proposed OEL for Mn in Welding Fumes

Our analysis indicates that, for derivation of an occupational exposure limit for Mn, there is no need to start with a POD as low as 77 μg/m^3 Mn when exposure to 142 μg/m^3 Mn in air (the POD based on US EPA's BMD approach from the battery facility worker study by Roels *et al*. [1992]) is also associated with normal levels of Mn in the brain. Similarly, there is no evidence to support the application of a UF of 3 for increased bioavailability of Mn in welding fumes compared to other Mn occupational exposures.

Overall, the best and most current available scientific evidence suggests that airborne occupational exposure to Mn as an 8-hour TWA of 140 μg/m^3 (and likely as high as 200 μg/m^3) for Mn in welding fumes would not produce adverse neurological effects in welders.

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