Review of Scientific Evidence Related to Potential Toxicity from Occupational Exposure to Manganese

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Manganese

- Essential nutrient important for the formation of healthy cartilage and bone and for brain development
  - Homeostatic mechanisms important for maintaining appropriate Mn levels in the body
- Normal levels of Mn in the human brain range from 0.24 – 0.64 µg/g (Ramoju et al. 2017)
  - Information on "normal" levels is useful for informing no effect levels and potentially toxic levels (unlike other toxic agents, e.g. lead)
- Most common effects at high exposure concentrations are neuromotor (tremor, hand-eye coordination)
  - Chronic exposure to levels of Mn in air > 2,000 µg/m³ is known to cause a disabling syndrome called "manganism" (dull affect, altered gate, tremor)
- Lower occupational Mn exposures → subtle neurological effects
Continuum of Responses from Biomarkers of Exposure to Adverse Effect

Lower exposure concentration ➔ Perturbation ➔ Early cellular changes ➔ Later cellular changes ➔ Apical effect ➔ Higher exposure concentration

Exposure ➔ Perturbation ➔ Early cellular changes ➔ Later cellular changes ➔ Apical effect

Biomarkers of Exposure ➔ Biomarkers of Adverse Effects

Non-adverse ➔ Adaptive ➔ Compensatory

Less likely to be adverse ➔ Transient ➔ Early Precursor Responses/Effects ➔ Immediate Precursor Effects ➔ Reversible ➔ Irreversible Impairment ➔ No Functional Impairment

Adapted from Goodman, JE; Dodge, DG; Bailey, LA. 2010. Regul. Toxicol. Pharmacol. 58 : 308-322
"At the lowest exposure concentration (0.01 mg/m³ 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/m³, slight increases (~5%) in brain Mn concentration above background levels were observed during the inhalation exposure period."

1) 0.1 mg/m³ does not equate to a level that will cause neurological effects. Brain concentration within normal range (~0.5 ug/g)

2) Effect studies needed to identify levels of effect

Range of Normal Mn Levels in the Brain

Fig. 5. Predicted globus pallidus Mn concentrations following exposure to 0–1000 µg Mn/m³ in air for 8 h/day, 5 d/week up to 5 years. The shaded region represents background MnGP range based on human autopsy reports of 'healthy' subjects. Also shown are PODs used by ATSDR (2012) and Health Canada (HC, 2010) in derivation of minimum risk level (MRL) and reference concentration (RfC), respectively.


Background brain concentrations "based on human autopsy reports of healthy subjects"
## Current Mn Occupational No Effect Levels

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<tbody>
<tr>
<td><strong>Key Study</strong></td>
<td></td>
<td>Roels et al. (1992)</td>
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<tr>
<td><strong>Value</strong></td>
<td>20 μg/m³</td>
<td>142 μg/m³</td>
<td>77 μg/m³</td>
<td>20 μg/m³</td>
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<tr>
<td><strong>Basis for no effect level</strong></td>
<td>Regression equation from Roels et al. (1992) → 2.5% increased risk</td>
<td>BMDL$_{10}$ (10% increased risk)</td>
<td>BMDL$_{05}$ (5% increased risk)</td>
<td>BMDL$_{05}$ of 77 ÷ UF 3 (increased bioavailability from welding fume)</td>
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<tr>
<td><strong>Comment</strong></td>
<td>Not a scientifically robust calculation</td>
<td>Best methodology (US EPA Benchmark Dose Software)</td>
<td>US EPA methodology (OEHHA application of BMDL$_{05}$)</td>
<td>Best available science suggests no UF necessary.</td>
</tr>
<tr>
<td><strong>Mn level in brain</strong></td>
<td>All concentrations predicted to result in normal levels of Mn in the brain (Schroeter et al., 2011; Ramoju et al. 2017)</td>
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1. Uncertainty Factors (UFs) typically only applied when there is a question as to possible increased sensitivity AND inadequate evidence to suggest otherwise.
2. Decreasing from normal level → normal level. No health benefit.
Manganese Welder Neurological Effect Studies

• 25 welder studies evaluated subclinical neurological effects in welders and Mn exposure concentrations.
  - Bailey et al. (2017): OEL of 140 µg/m³ for Mn welding fume

• Majority of studies estimated mean exposure concentrations from a large range of exposures.
  - Mn exposures range from 2 – 9,300 µg/m³ across studies
  - Difficult to use mean concentrations from studies as an effect level or no effect level
  - Several recent studies do a more careful dose-response evaluation (Ellingsen et al. 2008; Ma et al. 2018; van Thriel et al. 2017)
Bowler et al. (2007) & Park et al. (2009) San Francisco-Oakland Bay Bridge Welder Study

- Evaluated cognitive test scores for 44 confined space welders
- Mean Mn exposure of 210 µg/m³ (range 110-460 µg/m³), with 55% exposed to > 200 µg/m³.
- Reported neurological effects in 40-80% of welders
- Study limitations:
  - No control group (used "test publishers' norms")
  - Exposure evaluation inadequate (1.5 years on bridge work; exposure history not considered [14 years prior welding exposure])
  - Results could be bias because of worker compensation litigation
- Conducted benchmark dose (BMD) modeling on effects data (US EPA software)
  - Derived BMDL₁₀ range = 72-104 µg/m³ (well above TLV of 20 µg/m³)

*ACGIH (2013) describes study results but not limitations
Laohaudomchok et al. (2011) Welder Study

• Study of neurological effects in 46 apprentice welders
• Median Mn exposure of 13 µg/m³
• Reported correlations between neurological effects (reaction time, mood) and Mn cumulative exposure

• Study limitations:
  ▪ No unexposed control group
  ▪ Exposure evaluation inadequate (monitor on shoulder, not breathing zone)
    ▪ Authors acknowledge that significant associations are largely dependent on 3 of the highest exposed welders (>90 µg/m³).
  ▪ Borderline to no significant association once highest exposed removed.

*ACGIH (2013) describes study results but not limitations
Summary of Key Mn Welding Fume Studies

- **Baker et al. (2015)**
  - No impact on normal Mn levels in body
  - No neurological effects (mean)
  - No neurological effects (top of range)

- **Pesch et al. (2012, 2017)**
  - No adverse effects expected

- **Baker et al. (2014)**
  - No impact on normal Mn levels in body

- **Schroeter et al. (2011)**
  - No adverse effects expected

- **van Thriel et al. (2017)**
  - No adverse effects expected
  - NOAEL range = 140 µg/m³

- **Ma et al. (2018)**
  - Possible NOAEL range

- **Ellingsen et al. (2008)**
  - No adverse effects expected

**NOAEL based on a mean/median = 140 µg/m³**
Top of Effect Concentration Range is Well Above Mean

Mn in welding fumes (µg/m³)

NOAEL

Effect level mean = 423 µg/m³ (204 – 2,000)

Possible NOAEL

Precise dose where neurological effects begin is unclear. Influence of higher exposed individuals (>200) unclear.

Effect level mean = 230 µg/m³ (50 – 410)

Ellingsen et al. (2008)

van Thriel et al. (2017)

Ma et al. (2018)
Mn Levels in the Brain at 140 vs. 200 µg/m³

"At the lowest exposure concentration (0.01 mg/m³ 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/m³, slight increases (~5%) in brain Mn concentration above background levels ...(> 30%) predicted at the higher exposure concentrations (> 1.0 mg/m³)"

Mn Levels in the Brain at 140 vs. 200 µg/m³

• If we assume 10% increase from 140 → 200 µg/m³
  ▪ 0.64 µg/g → (0.64 + 0.064 = 0.70 µg/g)

• 0.64 and 0.70 µg/g Mn in the brain are not very different (140 vs. 200 µg/m³)
  ▪ Within, or at least very close to, normal range of Mn levels in the brain

• Non-human primate studies suggest NOAEL of 200 µg/m³ Mn and 0.8 – 1.2 µg/g Mn in the brain (Han et al. 2008; Kim et al. 2013; Schroeter et al. 2012)

• Dose where effects occur is uncertain (>200 to >400 µg/m³)
Conclusion Regarding Mn OEL for Welding Fumes

• No need to start with a No Effect Level of 77 μg/m³ Mn when exposure to 142 μg/m³ Mn in air is also associated with normal levels of Mn in the brain

• UF for increased bioavailability for welders vs. other Mn occupations is unnecessary.

• Evidence supports Mn OEL of 140 (possibly as high as 200) μg/m³ for welding fume
  ▪ Three welder neurological effect studies; non-human primate welding fume studies
  ▪ Understanding of Mn essentiality and normal levels in the brain
Thank you!
Questions?