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

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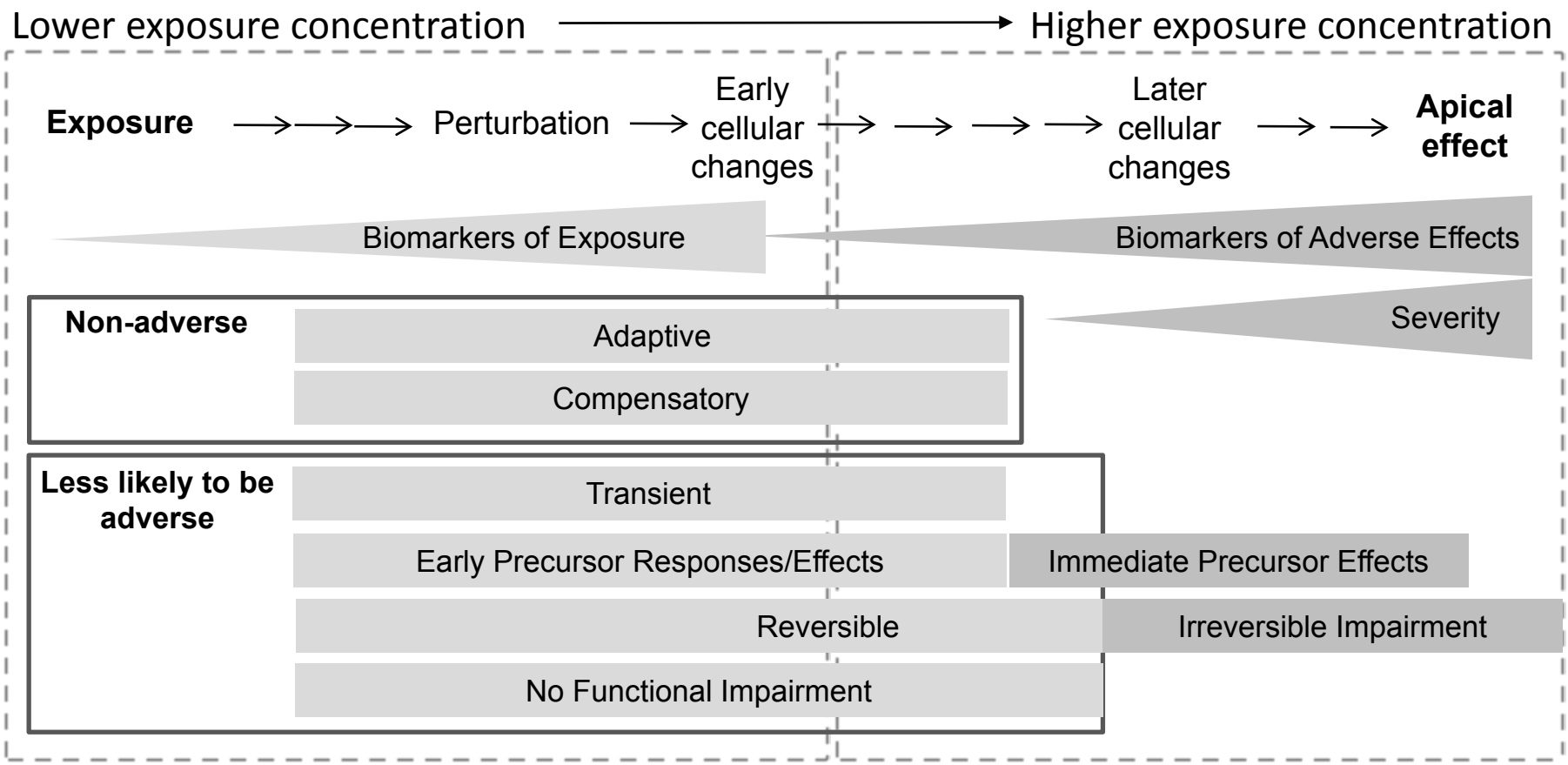
Manganese

- 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/m^3 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



Adapted from *Goodman, JE; Dodge, DG; Bailey, LA. 2010. Regul. Toxicol. Pharmacol. 58 : 308-322*

Mn Physiologically-Based Pharmacokinetic Model

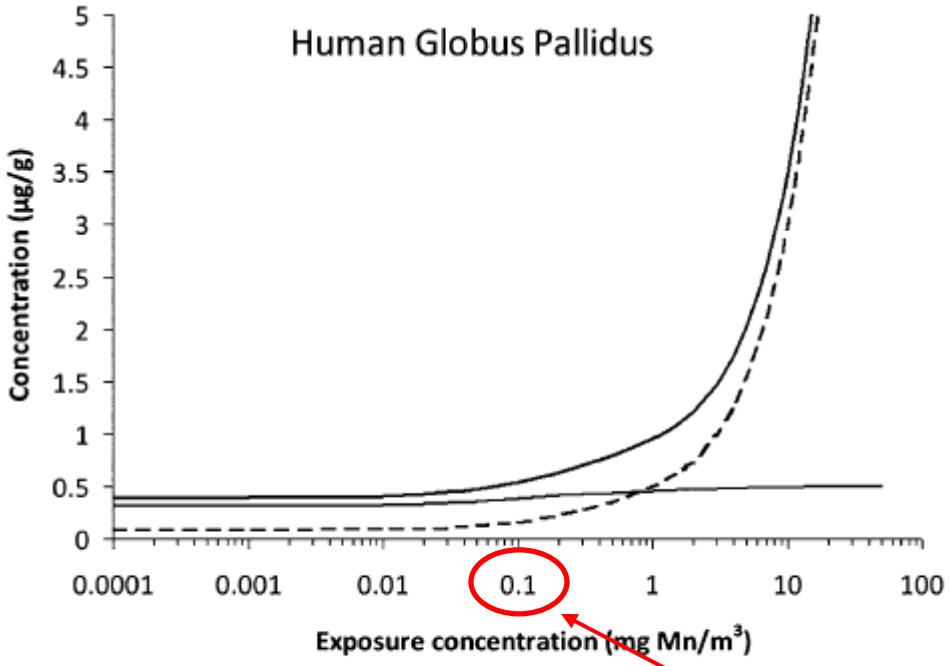


FIG. 13. Simulated end-of-exposure (90 days) Mn tissue concentrations of total (solid), free (dashed), and bound (gray) Mn in the monkey and human globus pallidus. The bound Mn fractions were 60 and 80% in the monkey and human, respectively, under normal dietary exposure.

Schroeter, JD; et. al. 2011 "Analysis of manganese tracer kinetics and target tissue dosimetry in monkeys and humans with multi-route physiologically based pharmacokinetic models." Toxicol. Sci.120 (2): 481-498.

"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

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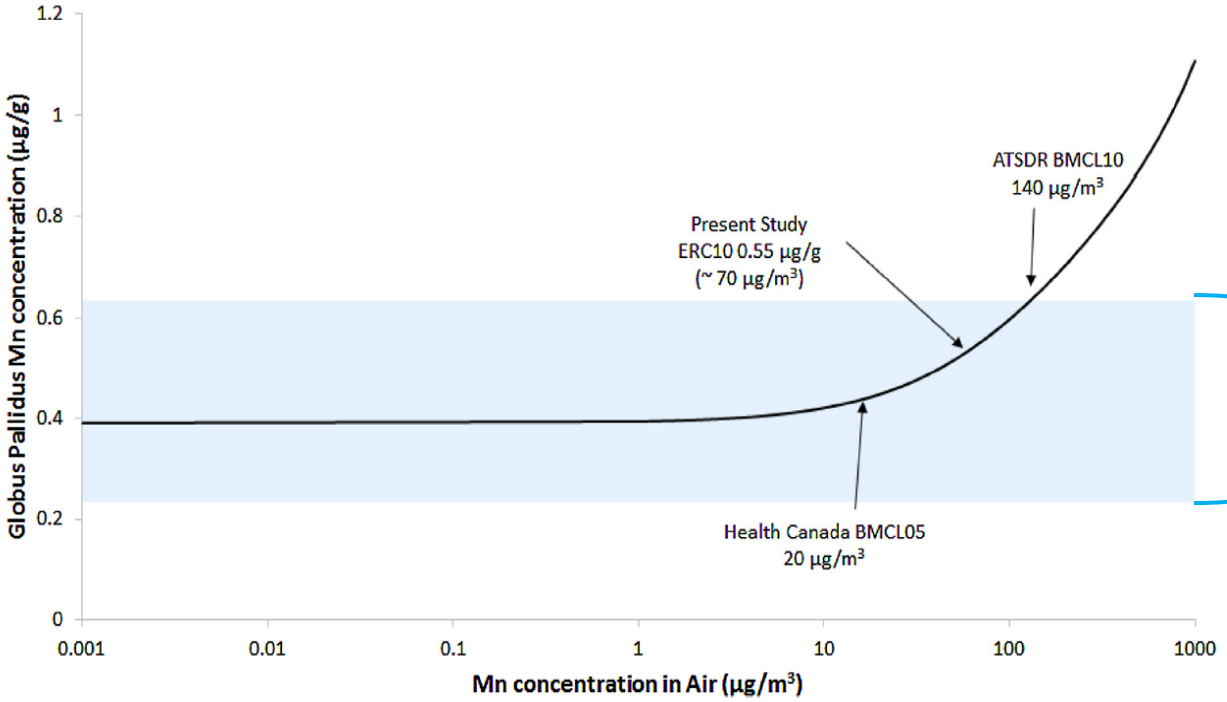
Range of Normal Mn Levels in the Brain



Normal Mn levels in the brain (0.24 – 0.64 µg/g)

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.

Ramoju, SP et al. 2017 "The application of PBPK models in estimating human brain tissue manganese concentrations." Neurotoxicology 58: 226-237

Background brain concentrations "based on human autopsy reports of healthy subjects"

Current Mn Occupational No Effect Levels

	ACGIH TLV (2013)	ATSDR MRL POD (2012)	OEHHA REL POD (2009)	DOSH Proposed PEL (2018)
Key Study	Roels et al. (1992) (battery facility workers study)			
Value	20 µg/m^3	142 µg/m^3	77 µg/m^3	20 µg/m^3
Basis for no effect level	Regression equation from Roels et al. (1992) → 2.5% increased risk	$BMDL_{10}$ (10% increased risk)	$BMDL_{05}$ (5% increased risk)	$BMDL_{05}$ of 77 ÷ UF 3 (increased bioavailability from welding fume)
Comment	Not a scientifically robust calculation	Best methodology (US EPA Benchmark Dose Software)	US EPA methodology (OEHHA application of $BMDL_{05}$)	Best available science suggests no UF necessary.
Mn level in brain	All concentrations predicted to result in normal levels of Mn in the brain (Schroeter et al., 2011; Ramoju et al. 2017)			

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/m^3 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/m^3 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/m^3 (range 110-460 µg/m^3), with 55% exposed to > 200 µg/m^3.
- 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 $BMDL_{10}$ range = 72-104 µg/m^3 (well above TLV of 20 µg/m^3)

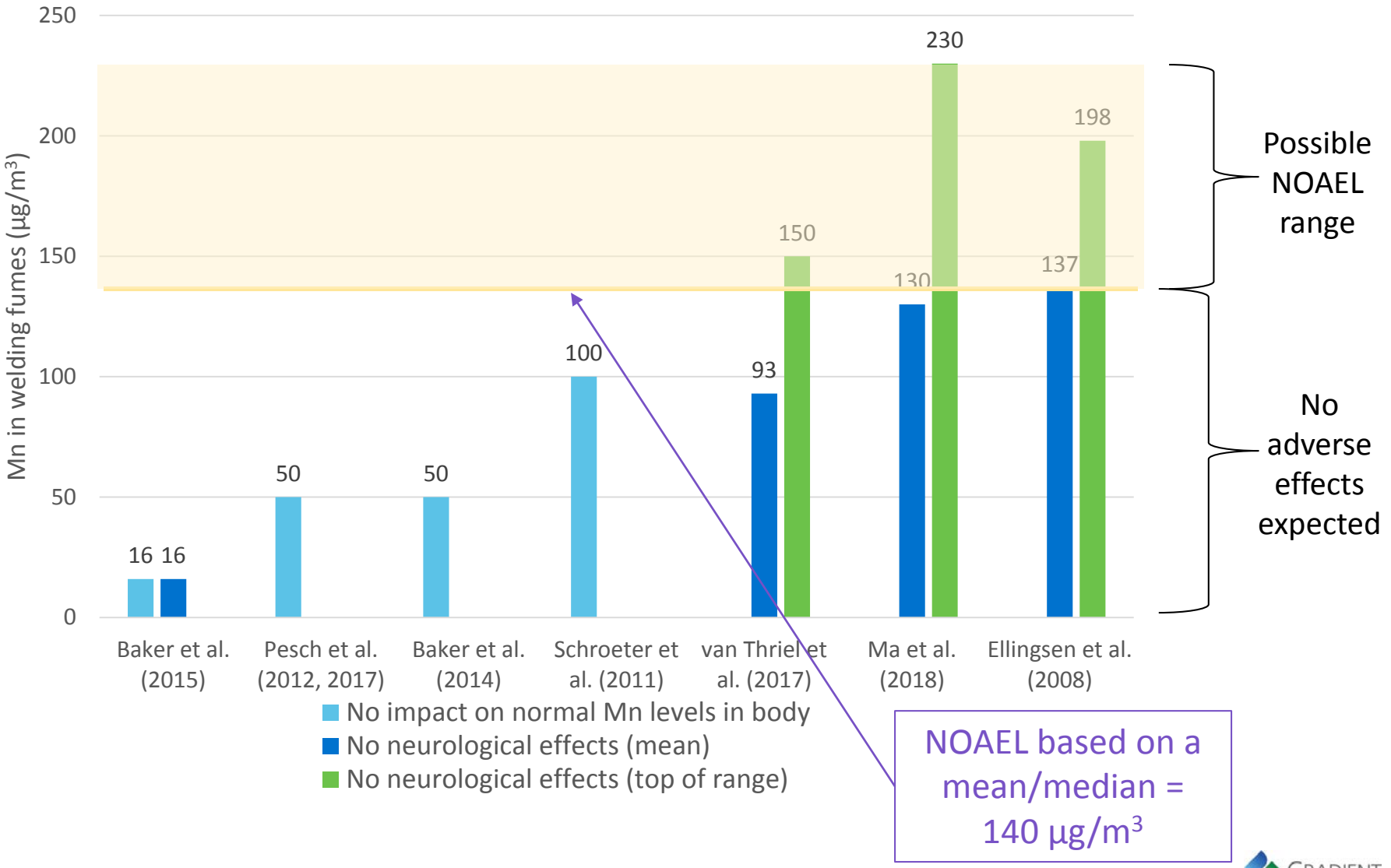
***ACGIH (2013) describes study results but not limitations**

Laohaudomchok et al. (2011) Welder Study

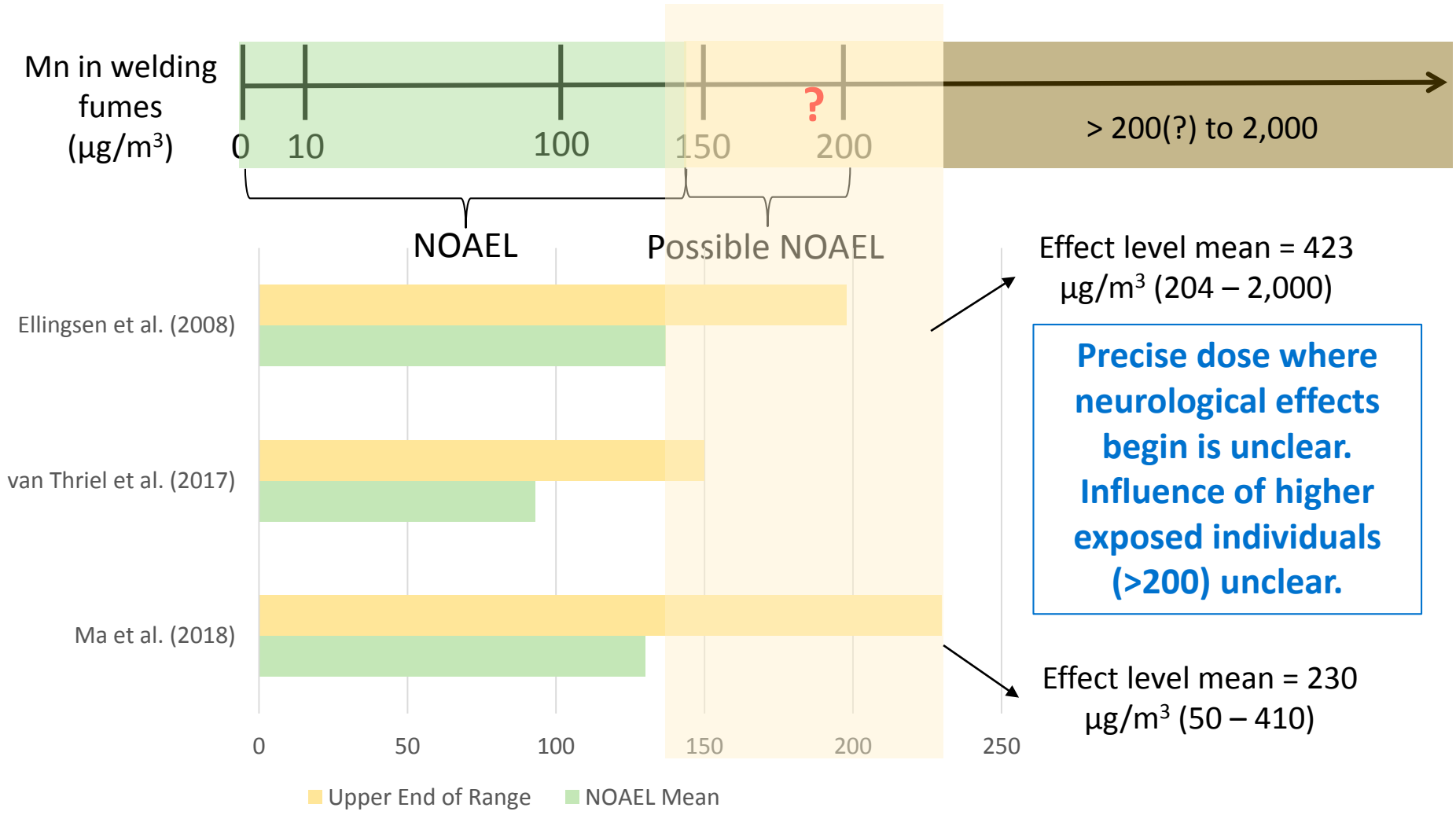
- Study of neurological effects in 46 apprentice welders
- Median Mn exposure of 13 µg/m^3
- Reported correlations between neurological effects (reaction time, mood) and Mn cumulative exposure
- **Study limitations:**
  - **No unexposed control group**
  - Exposure evaluation inadequate (**monitor on shoulder**, not breathing zone)
  - Authors acknowledge that significant associations are **largely dependent on 3 of the highest exposed welders (>90 µg/m^3).**
  - **Borderline to no significant association once highest exposed removed**.

***ACGIH (2013) describes study results but not limitations**

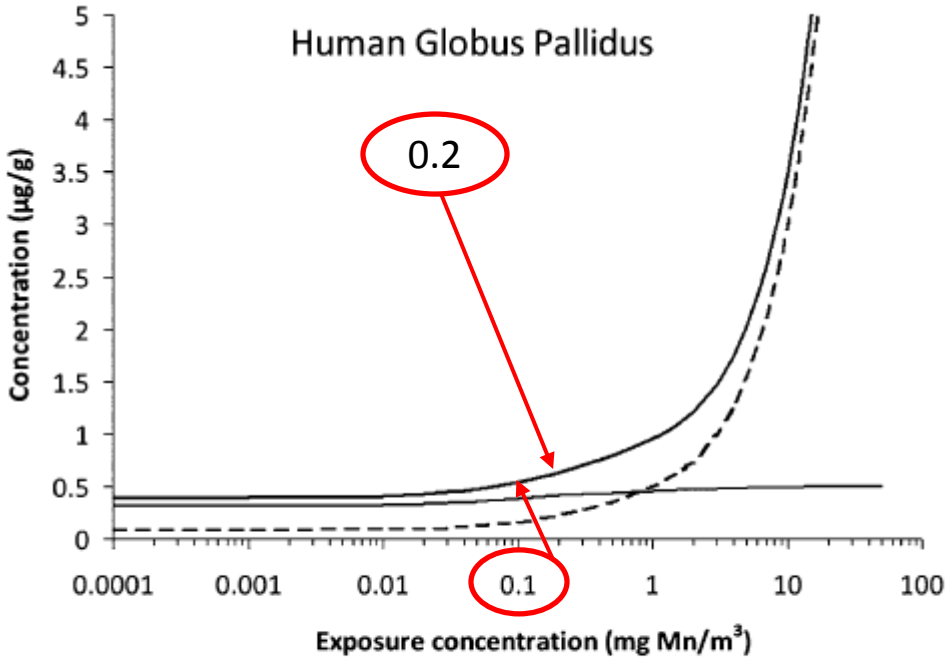
Summary of Key Mn Welding Fume Studies



Top of Effect Concentration Range is Well Above Mean



Mn Levels in the Brain at 140 vs. 200 µg/m^3



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Mn Levels in the Brain at 140 vs. 200 µg/m^3

- If we assume 10% increase from 140 → 200 µg/m^3
  - 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/m^3)**
  - Within, or at least very close to, normal range of Mn levels in the brain
- Non-human primate studies suggest NOAEL of 200 µg/m^3 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/m^3)

Conclusion Regarding Mn OEL for Welding Fumes

- No need to start with a No Effect Level of 77 µg/m^3 Mn when exposure to 142 µg/m^3 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/m^3 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?