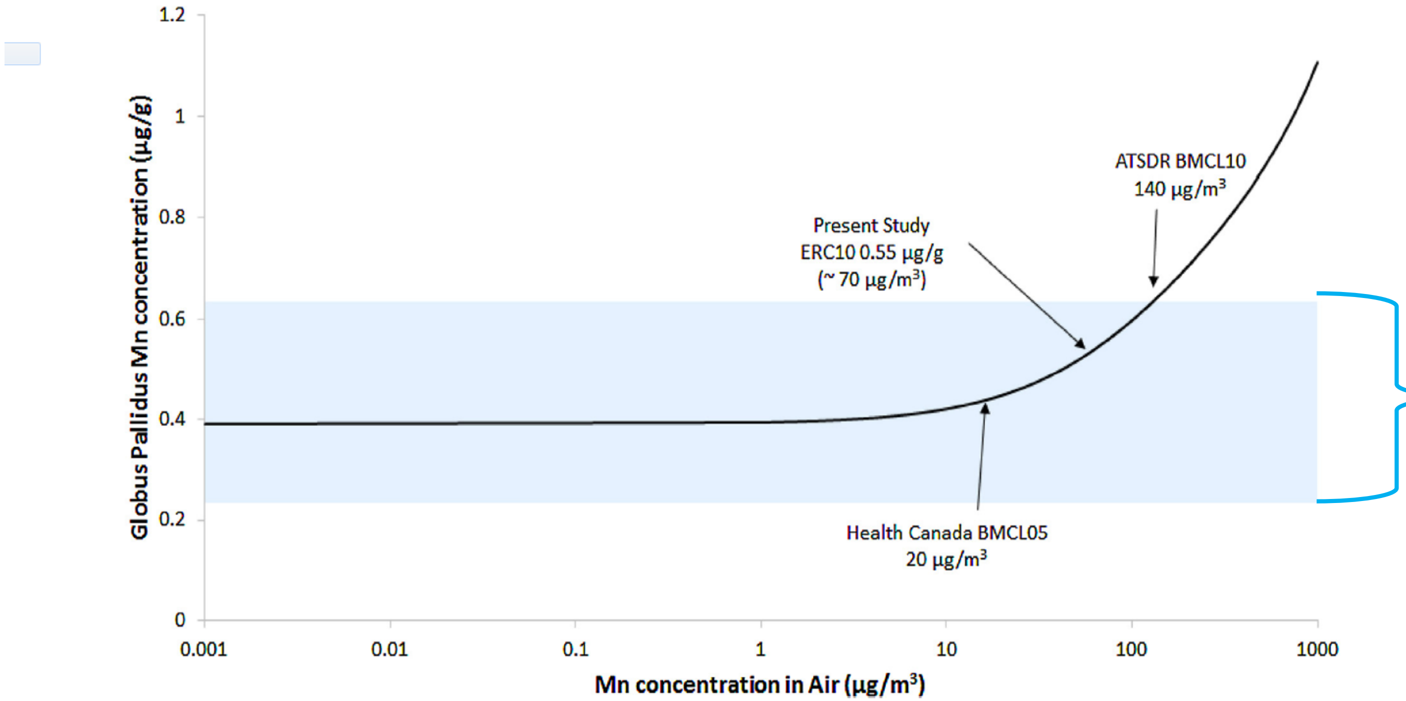
Topics from WSC presentation

- Normal Mn brain levels
- Solubility
- Uncertainty Factor
- Best Science

Slide from WSC presentation, 9/4:

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.

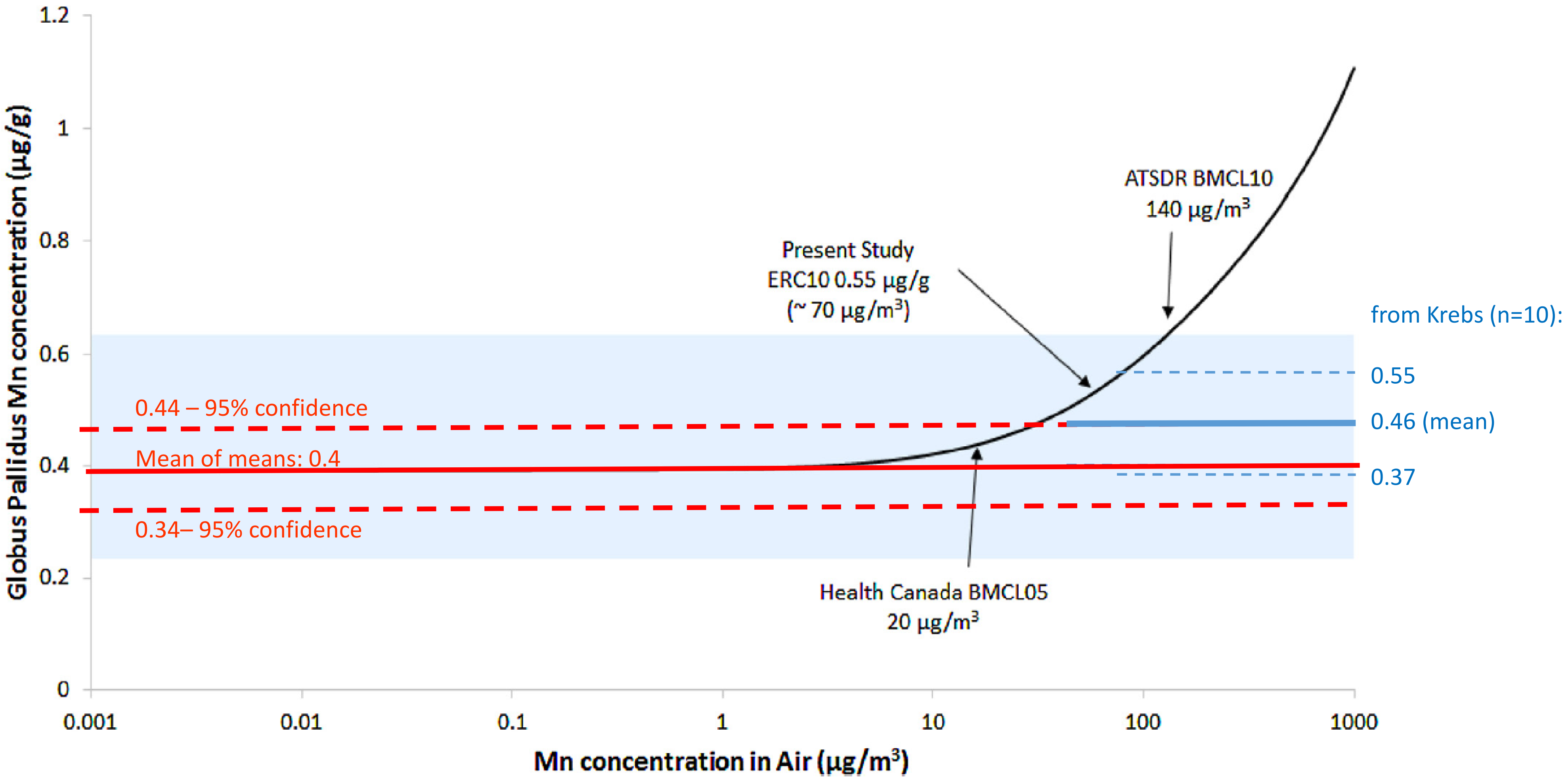
Ramoju, SP et al. 2017 "The application of PBPK models in estimating human brain tissue manganese concentrations." Neurotoxicology 58: 226-237

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

Study	N	Mean (ugrams/g tissue)				
Krebs	10	0.46				
Bush	5	0.44				
Maeda	1	0.42				
Goldberg	3	0.32				
Tracqui	3	0.39				
Markesbery	1	0.38				
Larsen	4	0.40				
Klos	5	0.25				
Layrargues	9	0.41				
					Confidence interval	
# of studies	9	0.4	0.06	0.05	**0.34**	**0.44**

Study	N	Mean	SD		Confidence interval	
Krebs	10	0.46	0.13	0.09	**0.37**	**0.55**

Confidence interval around the mean better indicator of “normal”



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Solubility: equivalent uptake of both Mn forms ($MnCl_2$ and MnO_2) from single dose

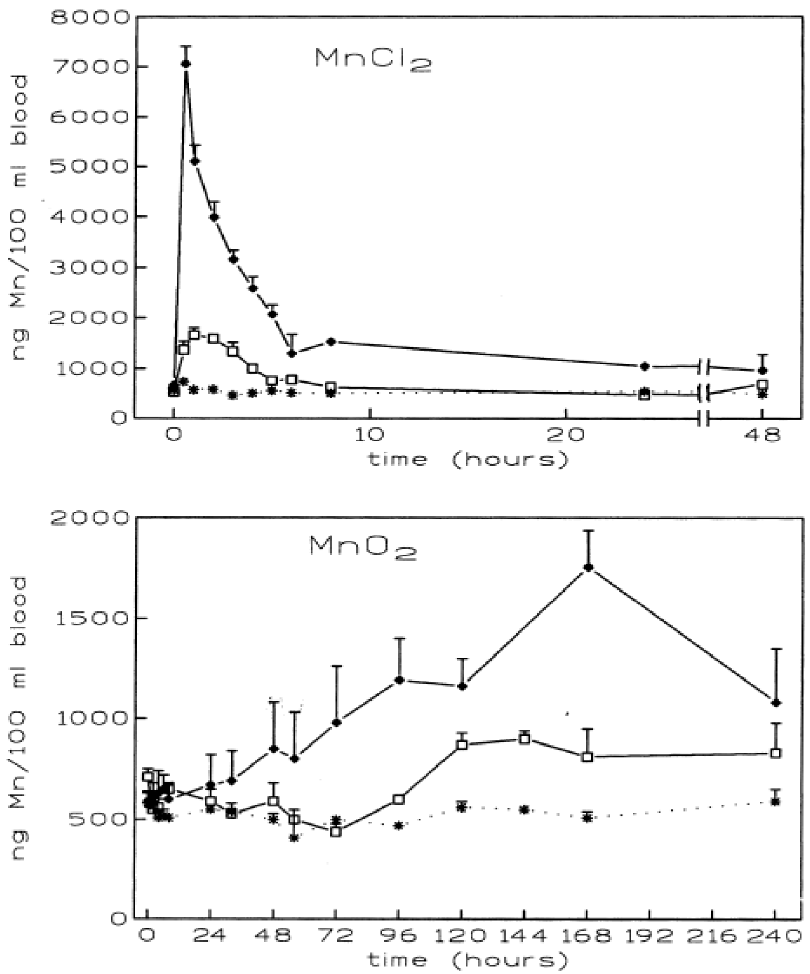
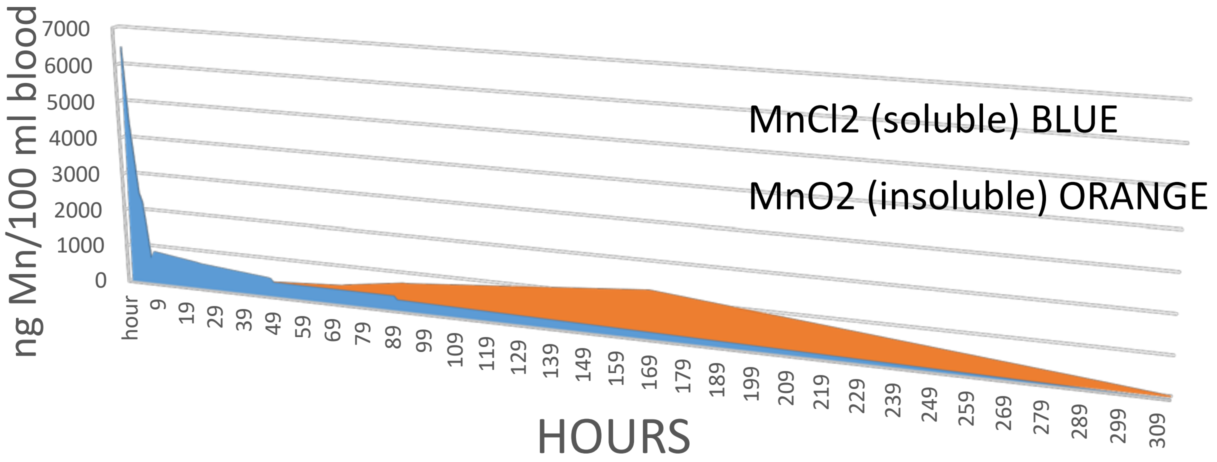
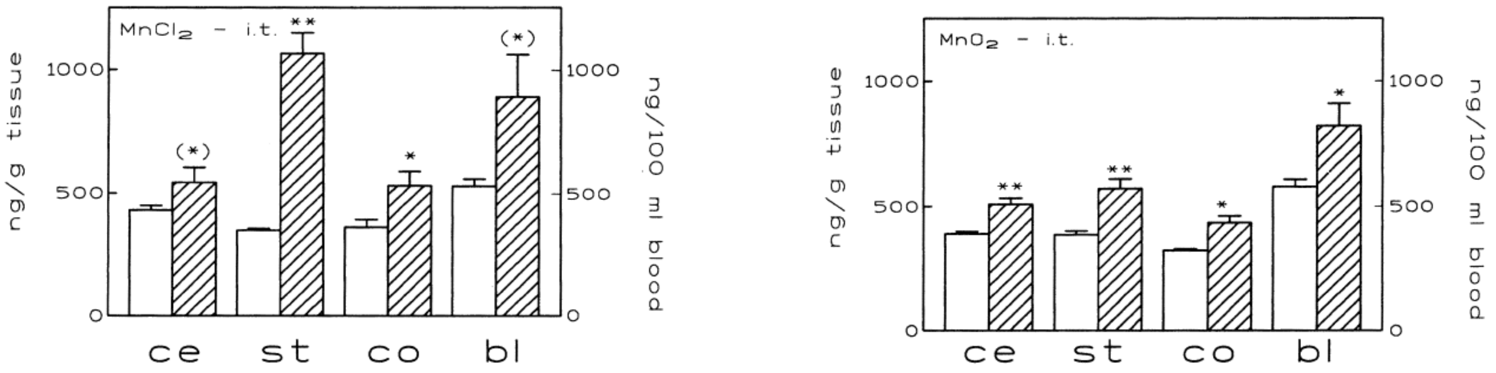


Fig. 3 Time course of Mn concentration in blood of rats after a single administration of either $MnCl_2$ or MnO_2 by intratracheal instillation (*filled diamonds*) of 1.22 mg Mn/kg body wt. or by oral gavage (*open squares*) of 24.3 mg Mn/kg body wt. Control rats were instilled with saline (*asterisks*). Each point represents mean ± SEM for three rats

AUC interpolated from ROELS, 1997





Concentration of Mn in cerebellum (ce), striatum (st), cortex (co) and blood (bl) In rats after 4 weeks of administration of saline (open) and MnCl2 or MnO2 (striped) by intratracheal instillation

Roels, 1997. *Influence of the route of administration and the chemical form on the absorption and cerebral distribution of Mn in rats. Arch Tox 71:223 – 230.*

SOLUBILITY (cont.): equivalent (though not different from controls) tissue levels at 0.03 mg Mn/m3.

All inhalation exposures were conducted for 6 h/day, 7 days/week for 14 consecutive exposure days (n = 12 rats per dose group.

Manganese exposures: Nominal $MnSO_4$ and Mn_3O_4 exposure concentrations were 0.092, 0.92 and 9.2 $MnSO_4/m^3$ and 0.042, 0.42 and 4.2 mg Mn_3O^4/m^3, respectively, corresponding to 0.03, 0.3 and 3 mg Mn/m^3. Target nominal particles size (MMAD) was approximately 1.5 – 2 um (GSD < 2).

Dorman, 2001: Influence of Particle Solubility on the Delivery of Inhaled Manganese to the Rat Brain: Manganese Sulfate and Manganese Tetroxide Pharmacokinetics Following Repeated (14-Day) Exposure

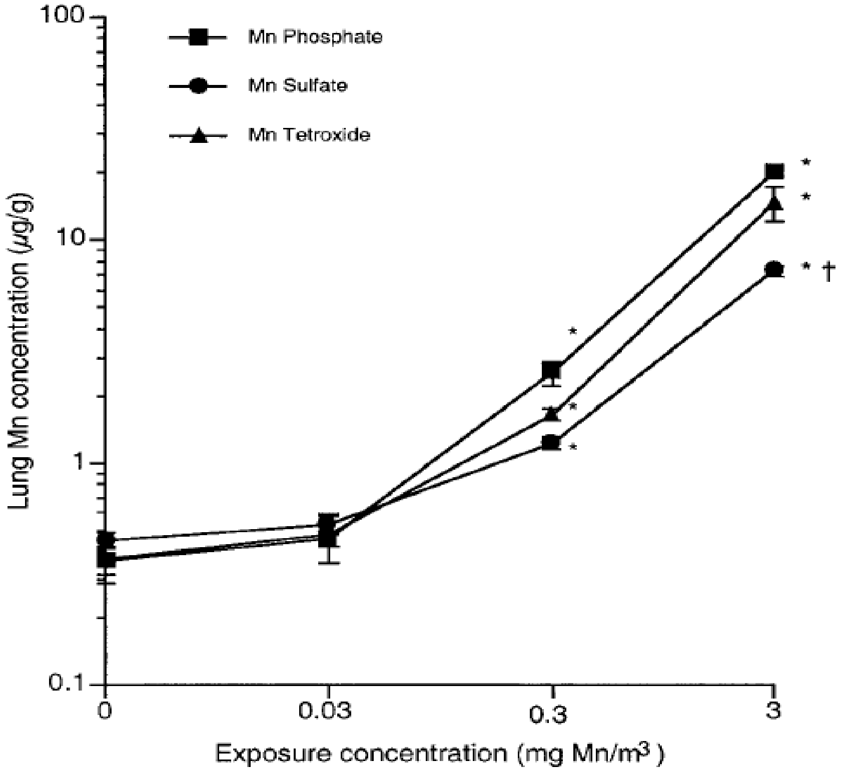


FIG. 1. Lung manganese concentrations (means ± SEM; µg Mn/g tissue wet wt) in rats exposed repeatedly to either $MnSO_4$ or Mn_3O_4. Data from Vitarella *et al.* (2000b) with similar manganese phosphate exposure conditions have been included for comparison. *Statistically significant increase in lung manganese concentration compared to air-exposed controls. †Statistically significant lower lung manganese concentration in $MnSO_4$-exposed rats compared with animals exposed to either the phosphate or the tetroxide form. (n = 6 rats/exposure concentration/chemical).

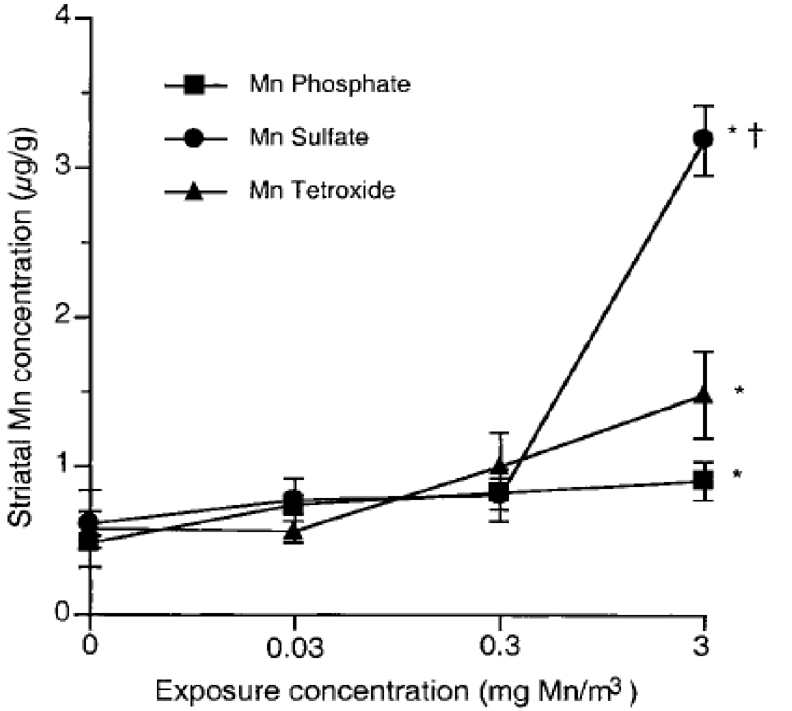


FIG. 3. Striatal manganese concentrations (means ± SEM; µg Mn/g tissue wet wt) in rats exposed repeatedly to either $MnSO_4$ or Mn_3O_4. Data from Vitarella *et al.* (2000b) with similar manganese phosphate exposure conditions have been included for comparison. *Statistically significant increase in striatal manganese concentration compared to air-exposed controls. †Statistically significant higher striatal manganese concentration in $MnSO_4$-exposed rats compared to animals exposed with either the phosphate or the tetroxide form. (n = 6 rats/exposure concentration/chemical).

UNCERTAINTY FACTOR

HEAC proposed a factor of 3 to scale the NOAEL from Roels study (smelters) to welders.
Table taken from Ramoju 2017 paper. This is the predicted deposition of inhaled particles based on mass median aerodynamic diameter (MMAD). Note that there is 2-3 more deposition of welder particles than smelter particles in the pulmonary region

			DEPOSITION FRACTION (%)		
Occupation	MMAD (µm)	GSD	Head	Tracheobronchial	Pulmonary
Battery worker	5	3	82.4	2.1	6.1
Smelter	2.6	4.5	61.8	3.7	7.3
Welder	0.54	2.4	24.5	6.6	15.1
Welder	0.33	4	21.1	9.8	20

Best Science – SCOEL and ACGIH recommend integration of results from multiple studies

From "Recommendation from the Scientific Committee on Occupational Exposure Limits for manganese and inorganic manganese compounds", SCOEL/SUM/127 June 2011, EU

Because of the heterogeneity of the data (different types of industry, different manganese compounds and particle sizes, different study designs and different neurofunctional measurements), and the inherent limitations of every individual study**, it is not possible to identify one single critical study that would be the best basis for setting the Indicative Occupational Exposure Limit Value (IOELV). Some studies identified a LOAEL, other a NOAEL.** Some studies relied on the respirable fraction; other on the inhalable or "total" (thoracic) fraction. A global approach using the most methodologically-sound studies, as used in the IEH Criteria document (2004) and a number of additional good quality studies published since this review was therefore considered to be the most robust and reliable approach. The studies by Roels et al. (1992), Gibbs et al. (1999) Myers et al. 2003b, Young et al. 2005, Bast-Pettersen et al. (2004) and Ellingsen et al. (2008) as well as Lucchini et al. 1999 in HC (2008) which showed adverse neurological effects and identified a point-of-departure (POD) in the dose-effect/response relationship may offer a basis for recommending an IOELV. Thus, a reasonable respirable IOELV of 0.05 mg/m3 can be recommended, and a reasonable inhalable IOELV of 0.2 mg/m^3 is also recommended. While recommending these values, SCOEL recognises that the overall systemic absorption of coarser particles (> respirable) is probably substantially lower than for the respirable fraction. Thus, SCOEL recommends both a respirable and an inhalable IOELV which would need to be observed conjointly.

From "Manganese, Elemental and Inorganic Compounds", ACGIH 2013.

I**n arriving at a TLV for Mn, consideration was given to the LOAELs derived from the studies of Bast-Pettersen (2004), Lucchini et al., (1999), Mergler et al. (1994) and Roels et al. (1992) which are, respectively, 0.036, 0.032, 0.038 and 0.036 mg Mn/m^3, indicating close agreement of these studies for a LOAEL in the range of 0.03 – 0.04 mg Mn/m^3 (respirable aerosol).** Data of Young et al. (2005) among South African smelter workers, and Park et al. (2006) were similar. A TLV-TWA of 0.02 mg Mn/m^3, respirable particulate matter, is recommended for manganese and its inorganic compounds to reduce the potential for preclinical, adverse, neurophysiological and neuropsychological effects on manganese-exposed workers. This TLV is 1.5 – 2.0 times lower than the range of LOAEL values observed, and near the lower end of the range found by Young et al. (2005). According to a statistical model of Roels et al. (1992), a level of 0.02 mg Mn/m^3 (respirable) would lead to impaired hand steadiness (detected with subtle tests but not clinically) in 2.5% of workers.

Issues with Ellingsen welder studies: sampling (2006) and neurobehavioral study (2008)

Air sampling – Ellingsen (2006) does not report respirable Mn.

“Exposure to welding fumes was assessed by employing 25 mm Millipore plastic cassettes (M000025A0) equipped with 5.0 mm pore-size polyvinyl chloride membrane filters (Millipore, Bedford, MA, USA, PVC502500). **These filter cassettes for the measurement of ‘‘total’’ dust were placed in the breathing zone underneath the welding helmet. The pumps employed were SKC’s Sidekick personal units operated at a constant flow of 2.0 L min_1 (SKC Ltd,** Dorset, UK). The airflow was measured at the beginning and at the end of each sampling period using a rotameter.”

Welding methods – Ellingsen (2006) reported workers used different welding methods with different total Mn concentration. Exposure misclassification?

“Three basic welding methods were used in this study: (1) In **Shielded-Metal Arc Welding** the heat generated melts a portion of the electrode tip, its coating and the base metal in the immediate area. Most conventional arc welding is done handheld by means of a coated consumable electrode. We have termed this method **‘‘manual welding’’**; (2) **Gas Metal-Arc Welding** shields the weld zone with an external gas or gas mixture. We have termed these methods **‘‘semi-automatic’’**; (3) **Fluxed-Core Arc-Welding** uses a tubular electrode filled with flux. The emissive fluxes that are used shield the weld arc from surrounding air, or shielding gases are used and non-emissive fluxes are employed. The welding process is easily automated with robotic systems. We have termed this process ‘‘**automated welding’’**”

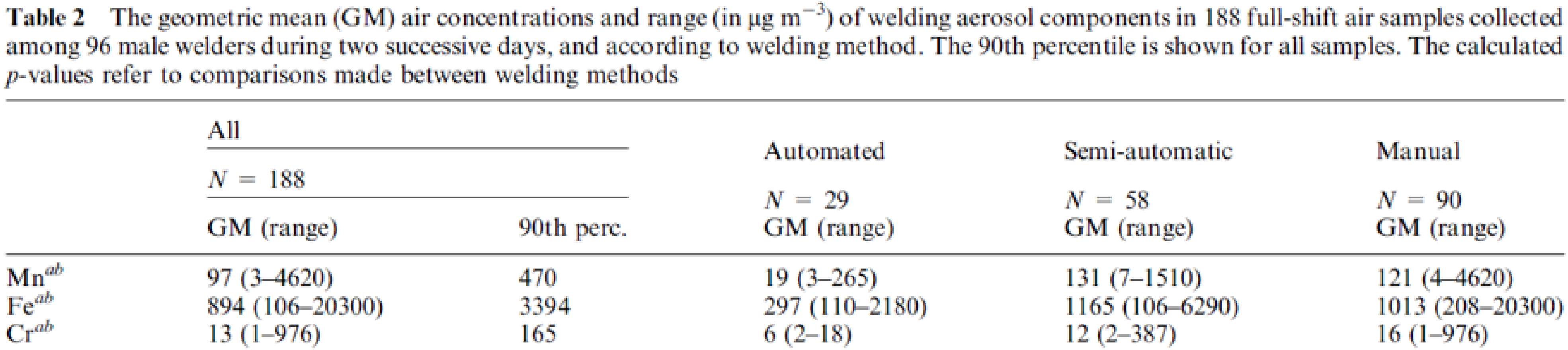


Table 2 The geometric mean (GM) air concentrations and range (in μg m^{-3}) of welding aerosol components in 188 full-shift air samples collected among 96 male welders during two successive days, and according to welding method. The 90th percentile is shown for all samples. The calculated *p*-values refer to comparisons made between welding methods

	All		Automated	Semi-automatic	Manual
	N = 188		*N* = 29	*N* = 58	*N* = 90
	GM (range)	90th perc.	GM (range)	GM (range)	GM (range)
Mn^{ab}	97 (3–4620)	470	19 (3–265)	131 (7–1510)	121 (4–4620)
Fe^{ab}	894 (106–20300)	3394	297 (110–2180)	1165 (106–6290)	1013 (208–20300)
Cr^{ab}	13 (1–976)	165	6 (2–18)	12 (2–387)	16 (1–976)

Different welding methods produce different MMAD and lung deposition.

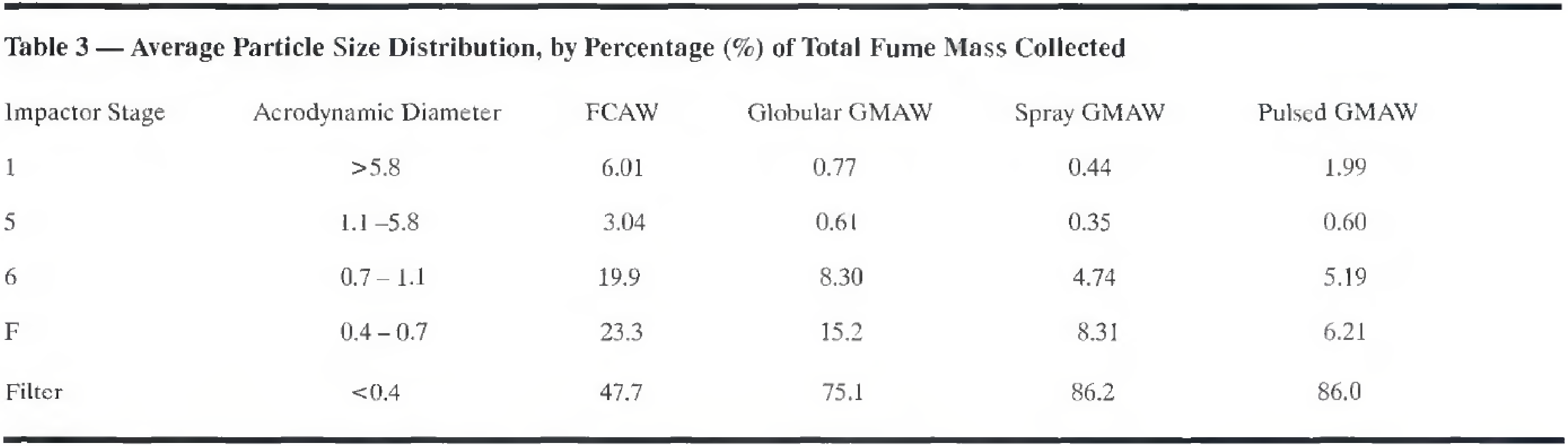


Table 3 — Average Particle Size Distribution, by Percentage (%) of Total Fume Mass Collected

Impactor Stage	Aerodynamic Diameter	FCAW	Globular GMAW	Spray GMAW	Pulsed GMAW
1	>5.8	6.01	0.77	0.44	1.99
5	1.1 –5.8	3.04	0.61	0.35	0.60
6	0.7 – 1.1	19.9	8.30	4.74	5.19
F	0.4 – 0.7	23.3	15.2	8.31	6.21
Filter	<0.4	47.7	75.1	86.2	86.0

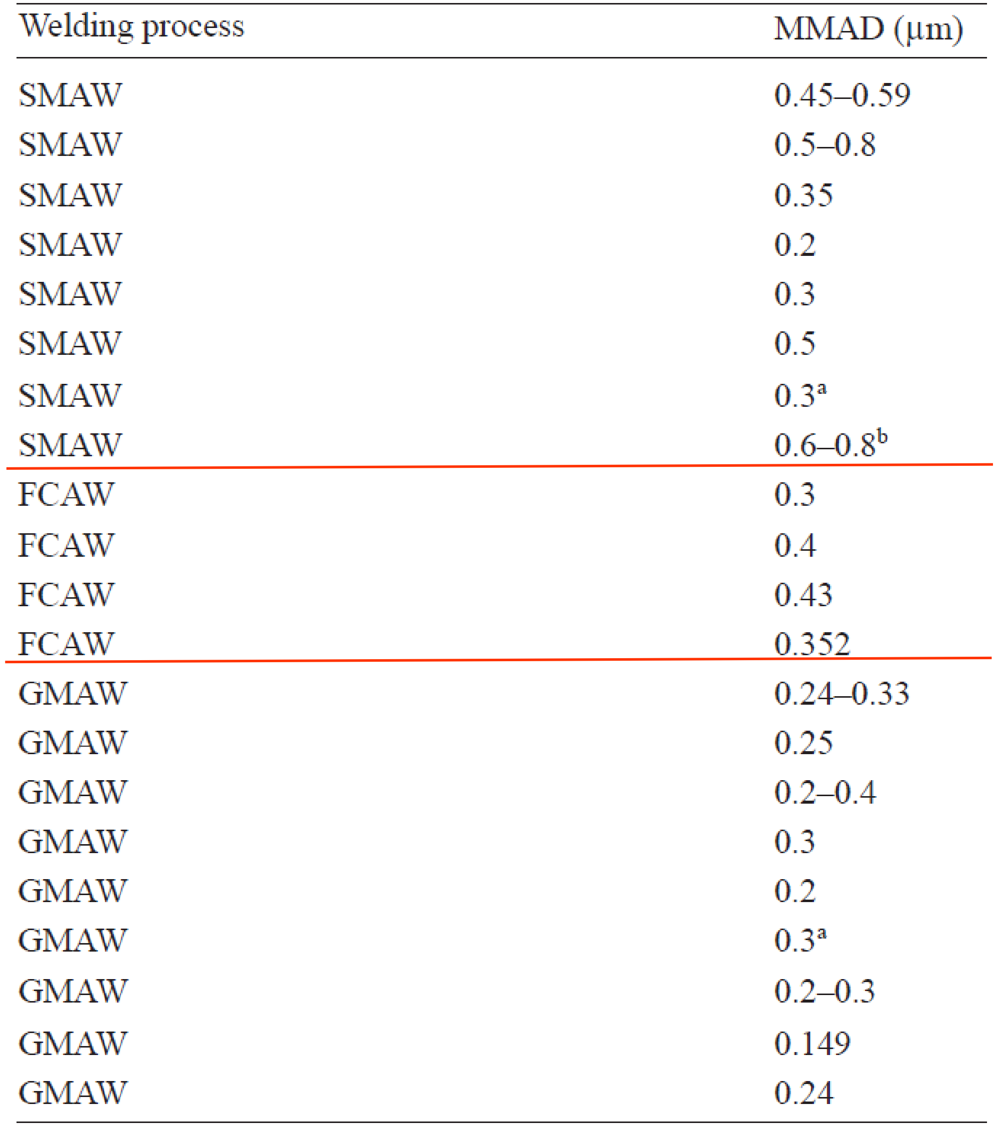
Jenkins 2005. Particle Mass Size Distribution of Gas Metal and Flux Cored Arc Metal Welding Fumes

Welding MMAD: SMAW > FCAW > GMAW

"Several other authors have proposed MMAD for GMAW and FCAW fumes to be in the range of 0.2 – 0.4 and 0.3 – 0.4 um, respectively (see Table 4). Moreover, particles generated from SMAW have been studied by Hewett (1995) who found that most particles had a larger MMAD (0.59 um) than particles in GMAW-generated fume (0.46 um). One possible explanation is that SMAW has a greater fume formation rate than GMAW. In that study, the specific surface area was found to be smaller for SMAW fumes than that for GMAW fumes."

Taube, 2013: Manganese in Occupational Arc Welding Fumes – Aspects of Physicochemical Properties with Focus on Solubility

Tabe 4: MMAD of different welding methods



Welding process	MMAD (µm)
SMAW	0.45–0.59
SMAW	0.5–0.8
SMAW	0.35
SMAW	0.2
SMAW	0.3
SMAW	0.5
SMAW	0.3[a]
SMAW	0.6–0.8[b]
FCAW	0.3
FCAW	0.4
FCAW	0.43
FCAW	0.352
GMAW	0.24–0.33
GMAW	0.25
GMAW	0.2–0.4
GMAW	0.3
GMAW	0.2
GMAW	0.3[a]
GMAW	0.2–0.3
GMAW	0.149
GMAW	0.24

Ellingsen 2008 reports doe-response found in two neurobehavioral measures

“Based on the regression equations in Table 4, the current welders were stratified into three equally large groups according to air-Mn or B-Mn, and compared with their age-matched referents within each stratum. The 32 welders with the highest B-Mn had poorer Digit Symbol test performance ($p = 0.01$) than their 32 age-matched referents (adjusted for education and age) (Fig. 1). Their respective AM B-Mn were 12.6 (range 8.7–23.5) mg/L and 7.5 (range 3.7–14.3) mg/L ($p < 0.001$). Dose–response was also found between the Finger Tapping test and the current air-Mn (Fig. 2).”

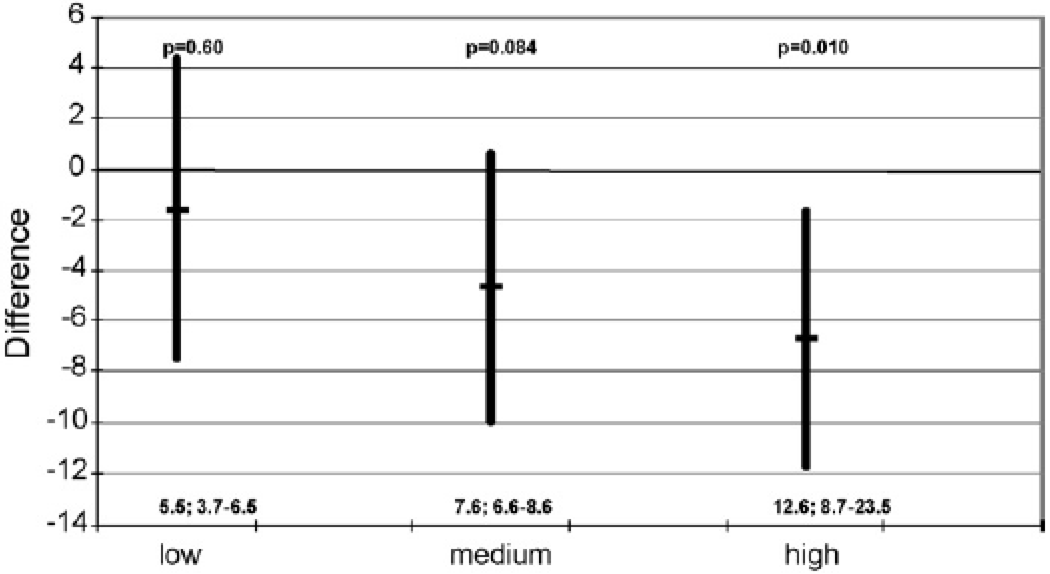


Fig. 1. The mean difference (and 95% CI) in the Digit Symbol test scores (adjusted for age and education) between welders and referents matched for age according to the level of B-Mn. The mean B-Mn (in µg/L) concentrations and ranges are shown.

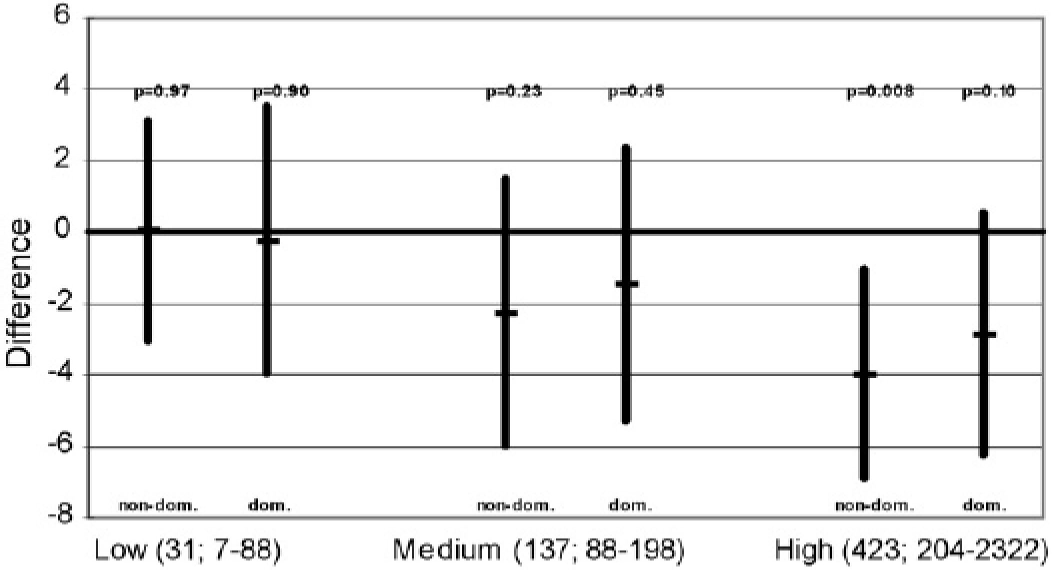


Fig. 2. The mean difference (and 95% CI) in the Finger Tapping test scores for the dominant (dom.) and non-dominant (non-dom.) hand (adjusted for age and smoking) between welders and referents matched for age according to the level of air-Mn. The geometric mean air-Mn concentrations (in µg/m^3) and ranges are shown in brackets.

Ellingsen, 2008: A neurobehavioral study of current and former welders exposed to manganese