

Cal/OSHA Draft Substance Summary for the December 12, 2017 HEAC Meeting

Substance name: Manganese (elemental and inorganic compounds, as Mn)

CAS: 7439-96-5

MW: 54.94

Synonyms: Mn

Molecular formula: Mn 54.94 g/mol

Structural formula: Mn^{2+}

ppm to mg/m³ conversion factors at 25 °C and 760 mm/Hg: 0.45 ppm = 1 mg/m³

GHS Classification (29 CFR 1910.1200): Flammable solids, category 2

GHS Label Elements:



Signal Word: Warning

Hazard Statements:

HE4* Acute Toxicity---Short-term high risk effects; H331 Toxic if inhaled

HE7* Nervous System Disturbances---Nervous system effects other than narcosis; H372 CNS damage

H228 Flammable solid.

*OSHA Health Effects Codes indicate the principal health effects of exposure to each substance. H statements are GHS Hazard statements.

Precautionary Statements: P210 Keep away from heat/sparks/open flames/hot surfaces - No smoking, P280 Wear protective gloves/protective clothing/eye protection/face protection, P370+P378 In case of fire: Use Class D dry chemical extinguishing agent for extinction.

Physical characteristics at room temp: grey-white metal

Special physical characteristics if any:

Flammability and other hazards: combustible, but dangerously flammable as powder or dust; finely dispersed particles may form moderately explosive mixture. Oxides from metallic fires are severe health hazard. Reacts slowly with water to release hydrogen gas.

Major commercial form(s): purified metal from ore and as a metallic alloy

Uses/applications: metal in aluminum and steel alloys, welding consumables, additive in unleaded gasoline, pigments, batteries.

Occupations with Potential Exposure to Manganese

Occupational exposures to manganese occur in welding, smelting and mining. There are no manganese mines in California, and relatively few smelters exist in California. According to the US Bureau of Statistics, there were 30,540 welders in California in May, 2016.

OEL recommendations

Title 8 PEL (2000):	Manganese and compounds, as Mn	0.2 ppm
	Manganese fume, as Mn	0.2 ppm & 3 ppm STEL
OSHA PEL (1973):	5 mg/m ³ Ceiling;	
ACGIH TLV (2013):	Elemental and inorganic compounds (respirable):	0.02 mg/m ³
	and (inhalable):	0.1 mg/m ³
NIOSH REL:	1 mg/m ³ TWA and 3 mg/m ³ STEL (1988); IDLH 500 mg/m ³ as Mn (1994)	

Other Recommendations:

Source and date	Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA REL 2008	8-hour: 0.17 µg/m ³ Chronic: 0.09 µ	Impaired neurobehavior: visual reaction time, eye-hand coordination, hand steadiness (Roels, 1992) Impaired neurobehavior: visual reaction time, eye-hand coordination, hand steadiness (Roels, 1992)	Using benchmark dose modeling of Roels (1992), the lower 95% confidence bound benchmark confidence level was 72 µ Used time-adjusted concentration of 26 µ and UF of 300.
HESIS PEL 2017*	Recommended PEL-TWA 0.007 mg/m ³ .	Based on the application of PBPK model to multiple studies on occupational workers exposed to manganese via inhalation; impaired neurobehavioral effects (Ramoju et al., 2017).	A PBPK dose-response model used data from multiple studies of manganese neurotoxicity. This model estimated a manganese concentration of 0.55 µg/g of tissue in the globus pallidus of the brain which is associated with a 10% extra risk of producing any adverse neurological responses in humans. Furthermore, according to this model, the air manganese concentration associated with this tissue concentration is about 70 µg/m ³ under occupational settings. This results in a PEL-TWA of 0.007 mg/m³ as follows after application of the cumulative uncertainty factor of 10 to account for intraspecies variability due to greater susceptibility of the developing brain <i>in utero</i> and anticipation of lasting effects as well as toxicokinetic variability due to exposure to manganese of different

			particle size. The current PEL-TWA is 0.2 mg/m ³ .
Prop 65	Not listed		
NTP	No evidence	NTP TR 428 NIH Publication No. 94-3159	Manganese sulfate monohydrate
EPA	IRIS RfC: 0.05 µg/m ³	Impaired neurobehavior: visual reaction time, eye-hand coordination, hand steadiness (Roels, 1992)	Derived a LOAEL of 0.15 from Roels (1992) and applied an UF of 1000.
IARC	Not classified		
EU	0.20 mg/m ³ (I) 0.05 (R)	SCOEL/SUM/127 June 2011	Recommended a “reasonable” OEL of 0.05 mg/m ³ respirable and 0.2 mg/m ³ inhalable. Acknowledged that the overall systemic absorption of coarser particles (> respirable) is probably substantially lower than for the respirable fraction and recommends that both a respirable and inhalable OEL be measured.
German MAK 2011	0.02 mg/m ³ 0.2 mg/m ³	Respirable fraction Inhalable fraction	

* Draft

Peer-reviewed journal articles used for proposed PEL

Mergler 1994

Study Type: Cross sectional, matched controls

Methods: Mn workers in a ferromanganese/silicomanganese alloy facility exposed to Mn dust from crushing/sieving and Mn fume from furnace. 115 exposed workers (95% of worker population) participated. 145 of 400 control workers not exposed to neurotoxins and paired with exposed workers based on age, educational level, smoking status, family size. After excluding for previous history of neurological illness, psychiatric disorder or treatment, or alcohol/drug abuse, 74 pairs were created. The following examiner- and computer-administered neuropsychological test batteries were implemented to assess six neurological categories: motor function range, sensory function, speech initiation and regulation, cognitive flexibility, attention/concentration/memory and mood states. Exposure measurements were obtained by personal monitoring of total dust and stationary environmental sampling of respirable and inhalable dust. Blood and urinary samples were obtained. Comparison of test scores were performed on the pair differences.

Results: 8-hr environmental measure were log-normally distributed ranged from 0.014 to 11.48 mg/m³ and respirable Mn ranged from 0.001 to 1.273 mg/m³. Interpair differences for whole blood Mn were highly significant (p= 0.0001) while no interpair difference was observed for urinary Mn. Of the six neurological categories tested, the number significant differences observed between exposed and controls of the total tests applied were: Motor function: 8/21; Sensory 1/10 (olfactory); cognitive flexibility (2/4); attention/concentration/memory 0/9; mood states: 4/6. On the neuropsychological and neurophysiological test batteries, the most prominent differences were observed on the tests of motor function, particularly those which required the person to perform coordinated, sequential, alternating movements at maximal speed. This type of movement is mediated by the central nervous extrapyramidal motor system which is especially vulnerable to manganese poisoning.

Bast-Petterson 2004

Study Type: Cross-sectional, matched controls

Methods: 100 production and maintenance workers from three ferro–manganese (FeMn) and silico–manganese (SiMn) alloys plants (mean exposure years = 20.2). Controls from similar plants where Mn not used and matched for age. Exposure characterized by 3 days of personal, full-shift monitoring of inhalable and respirable Mn. Symptoms and tests of cognitive, tremor, and motor function were obtained. Blood and urine samples were obtained.

Results: Blood and urine Mn and blood Pb were higher in the exposed groups than the controls. The inhalable and respirable Mn concentrations were 0.301 and 0.036 mg.m³, respectively (geometric mean). There were no differences in the symptoms between exposed and controls (0/7 of cognitive tests (0/11)). Differences between exposed and controls in the tremor (3/8) and motor (1/13) were observed. An association between smoking and tremor was also observed. When separated into exposure groups according to blood Mn levels (<157, 157-203, and > 203 nmol/L) statistical differences in tremor results were observed between the highest exposed workers and control. After adjustment for smoking and age, several measures of steadiness and tremor were significantly greater in exposed workers compared to controls.

Roels, 1992

Study Type: Cross sectional, matched controls

Method: Dry alkaline battery plant. 92 young workers (mean age 30) with 5.3 years of Mn exposure volunteered and were age matched to control workers not exposed to neurotoxins or lung irritants. Participants only chosen for study if blood, zinc, cadmium and mercury were in normal ranges. Exposure determined by personal samplers for total and respirable dust. Questionnaire responses (neurovegetative complaints, respiratory symptoms, medical history) whole blood and urine were obtained from both groups. Lung function assessed by recording maximal expiratory volume curves. Neurofunctional examination consisted of measurements of memory, visual reaction time (VRT), hand steadiness (HST) and eye-hand coordination (EHC).

Results: Geometric means of Mn air concentrations were 0.948 mg/m³ total and 0.215 mg/m³ respirable dust. Neither blood Mn nor urine Mn correlated with lifetime-integrated exposure concentrations calculated from individual total and respirable Mn dust measurements. No significant effect of Mn on spirometric parameters was observed between the groups. Mn workers had a significantly longer VRT over multiple testing periods compared to controls. EHC measures in Mn workers were significant different from controls. Memory scores between the two groups were not significantly different though Mn workers performed less well. There was a systematic tendency towards higher mean HST scores in Mn exposed groups compared to controls.

Roels, 1999

Study Type: Prospective of Roels 1992 cohort

Methods: To extend health surveillance of 1992 cohort with neurobehavioral testing, same methods carried forward in 8-year study. Under improved hygiene conditions leading to declines in Mn exposure, the early neurobehavioral dysfunction observed in 1992 study was tracked. Three exposure groups followed – high (14), medium (55) and low (23). Controls (24) were ex-Mn workers with ECH, HST and VRT results available at time of cessation of Mn exposure. Another control group (39) consisted of controls from 1992 study and was followed to assess effect of aging as confounder on EHS, HST and VRT.

Results: The Mn cohort declined from 92 to 34 over course of the study. Yearly mean total dust declined over the 8-year period from 0.795 mg/m³ to 0.250 mg/m³, a significant time trend with a more pronounced decline in the last 3 years of the study (0.650 to 0.250). Time course of the EHC had a biphasic pattern--decline from year 1 to 3 followed by an increase over the remainder of the study. This was observed in all three exposure groups. HST and VRT did not show consistent variation of significant time trends over the course of the study as the Mn concentration declined. HST was significantly different between exposure groups when Mn concentration were highest in the first 3 years of the study. For the second control group (ex-Mn workers removed from exposure), mean EHC values remained below that of controls however 80% improved. HST and VRT did not differ significantly over the course of the study and remained worse than controls.

Meyers 2003

Study Type:

Methods: Survey of 589 production workers at Mn smelting plant on compared with 67 control from electrical assembly plant. Exposure estimates were based on 310 personal inhalable dust measures. A cumulative exposure index (CEI) in mg years/m³ for inhalable dust was calculated for each subject by summing the products of the average inhalable concentration (using arithmetic means) for each job worked by the subject and the number of years this activity was performed. An average exposure intensity (INT) for all years worked was calculated by dividing the CEI by total years of service in the smelter works in mg/m³.

Results: Average CEI was 16.0 +/- 22.4 mg/m³ - year inhalable and the INT average 0.82 +/- 1.04 mg/m³ in smelter workers. Controls had no Mn exposure were younger and more educated. Significant differences between workers and controls were observed for tests of motor performance, visual retention, digit span and digit symbol tests. The digit test showed showed significant trends with increasing CEI levels. Mean visual reaction time did not differ between exposed and unexposed groups. Finger tapping with dominant and nondominant hands showed only marginal significance.

Young, 2005.

Study Type:

Method: Analysis of Myers 2003 using respirable Mn measurements to characterize exposure. 98 personal respirable samplers used to characterize exposure and exposure matrices developed to assign individual respirable particle exposure. CEI and INT calculated as in Meyers 2003. Results of 11 (motor function, response speed, memory and subjective symptoms) were analyzed by multiple linear and logistic models used with adjustments for age, years schooling past job exposure to neurotoxins previous head injury and language. 502 exposed workers were grouped into 5 exposure categories based on INT values ranging from 0 to 0.02 mg/m³.

Results: CEI was 0.92 mg/m³ - yr and INT averaged 0.058 mg/m³ respirable (0.003 - 0.51 mg/m³). When compared to the controls, the exposed workers were significantly different in 7 of 11 tests. Clearer exposure-response relationships were apparent using the INT for respirable fraction. Digit span, digit symbol score, and tapping with dominant or nondominant and showed increasing effects with increasing exposure levels but for all other tests there was not a significant trend between response and exposure category.

Gibbs, 1999

Study Type: Case-control study

Methods: 75 workers at Mn alloy plant matched to controls never exposed to Mn. Medical surveillance consisting of measurements of tremor, motor speed, and neuropsychological symptoms collected from both groups prior to start of the study. A job matrix of 12 categories was created and exposure determined from 63

full shift personal samplers of total and respirable particulate. Cumulative exposure to respirable and total Mn dust was estimated for each employee for 30 days, 12 months and the worker's employment history prior to the neuropsychological testing.

Results: Negative study. No differences observed between controls and exposed.

Bowler 2007

Study Type: Retrospective

Method: 43 welders in confined small spaces during construction of the Bay Bridge project over a two—year period. After two-year period, workers given a neuropsychological test battery and neurological, pulmonary, and psychometric (olfactory and visual) examinations. Measured and estimated air concentration were compiled by welding type and a cumulative exposure index calculated for each welder. Blood and urine samples were obtained. Multiple regression analyses performed to examine dose-effect association between neuropsychological/physiological test scores and blood Mn or CEI,

Results: Air concentrations ranged from 0.11 to 0.46 mg/m³ during 76% of the works shifts and 55% exceeded the standard of 0.2 mg/m³ for 8-hr time weighted average. Over the course of the study, FEV1 decreased by 7%, FVC by 2% and the FEV1/FEC ratio by 21.2%. 24 of 46 neuropsychological testing results were indicated a prevalence of welders with impaired performance at least twice as large as expected. Impairment in neurological and sensory scores in welders were 38.5-61.5 % (hand tremor intensity) and 51.4 % (postural sway). 88% of welders performed below individually matched population controls in olfactory testing. Significant dose-effect relationships between neuropsychological variables and blood Mn or CEI were found with covariates of years welding before the study and age, years of education and ethnicity before adjustment. For blood Mn, significant associations were obtained for IQ, cognitive flexibility, working memory and attention. For CEI, significant associations were obtained for verbal IQ, working memory and concertation/learning, memory and verbal skills.

Laohaudomchok 2011

Study Type: Volunteer study

Method: Apprentice welders recruited from welding school 46 completed questionnaire and neuropsychological testing. Students equipped with personal monitors with 2.5 micron cut point. Determined Mn concentration divided by half the assigned protection factor of the respirator used. Samples were collected to represent major tasks and a cumulate be exposure index over 12 months was calculated using welder reports of tasks and total hours)(mg/m³-hr). Welding history prior to study was calculated in a similar manner and a CEI calculated. Neuropsychological tests were administered to assess sustained attention, motor performance (reaction time and omission errors) and mood. Neuropsychiatric effects were assessed by a non-verbal profile of mood state questionnaire. 46 welders with past exposure history completed at least one neuropsychological testing and 24 welders has per- and post—shift neuropsychological testing.

Results: Airborne PM_{2.5} concentrations ranged from 0.057 to 3.04 mg/m³ on welding days. The airborne Mn concentrations ranged from 0.004 to 0.137 mg.m³ (median 0.129 mg/m³) on welding days and from 0.00012 - .000166 mg/m³ on non-welding days. Mn-CEI for the 12 months was 0-24.14 mg/m³ (median – 4.19 mg/m³-hr) and for total work history 0.1- 122.7 mg/m³ (median 14.73 mg/m³). Total work history CEI was significantly associated with worse attention span (p = 0.01) while 12 month CEI was not (p=0.10). In general, both 12-month and total work history CEI were significantly associated with worse mood. Neuropsychological testing pre- and post-shift indicated that Mn exposure was significantly associated with worse handwriting stability.

HEAC Health-based assessment and recommendation

Neurological effects are the most sensitive toxicological endpoint for manganese exposure. Studies with exposed workers show that the neurological effects of Mn are wide-ranging – cognitive, motor and mood – and are a consequence of cumulative exposure. The onset and reversibility of these effects also vary with subclinical effects appearing relatively quickly (less than 3 years exposure).

The two cited longitudinal studies (Roels/Roels; Meyers/Young) represent two of the best-characterized cohorts in terms of Mn exposure characterization, multiple neurological measures and follow-up. Based on these and other studies, LOAELs of approximately 0.035 mg/m³ respirable Mn were estimated by ACGIH (2009). Based on these studies, ACGIH has proposed 0.02 mg/m³ respirable and 0.1 mg/m³ inhalable as a TLV. The TLV assessment acknowledged that this level would not prevent all neurological risk.

The major uncertainty of this estimate is that it is based on studies of mixed sources of Mn particulate (smelting, alloy production and battery manufacture). Particle size is a primary factor in Mn toxicity and these sources are known to produce wide particle size distributions and concentration ranges. Many of these studies only measured total particulate and did not measure the respirable Mn fraction. Welding, the most probable exposure for California workers is known to produce a significantly higher fraction of uniform respirable particles than the other Mn processes, of which a large fraction is sub-micron in size. These particle characteristics make Mn fume more bioavailable for pulmonary deposition and absorption. A comparative brain imaging study found greater Mn levels in more brain regions of welders compared to smelter workers even though the cumulative exposure intensity of the welders was half that of the other group (REF). Of the cited studies, those by Bowler and Laohaudomchok are exclusively with Mn welders and in these studies, the onset of neurological and pulmonary effects over a relative short exposure period of time (< 2 years) was observed. In contrast, in the study of Mn smelter workers exposed to similar Mn concentration over 2.5 years (average), no neurological effects were observed. (Cowers, 2009).

Roels (1992) is widely used to determine risk-based estimates of Mn exposure. The average exposure interval of workers in that study was 5.5 years (0.02 – 17 y range). An 8-year follow-up study with the same cohort (Roels, 1999) conducted under declining Mn concentrations found that neurological deficits (eye-hand coordination, hand steadiness and visual reaction time) persisted for the middle and high exposed workers but that only eye-hand coordination returned to control levels in the low-exposed group. The original cohort declined from 92 to 37 workers over the course of the study, by the end of which the mean exposure interval of the workers was 14 years (9 – 24). Given that most of the effects observed in the first phase of this study carried through the next study, it would be appropriate to consider Roels (1992) as a chronic study and not apply a subchronic uncertainty factor in risk-based estimations.

The perinatal and postnatal developmental effects of Mn are a growing concern. While Mn is an essential element, Mn has been characterized as having an “inverted U-shaped dose response curve” – producing detrimental effects at low and high Mn levels. No developmental effects (malformations, low-birth weights, cognitive abilities, etc.) have been directly associated only with prenatal Mn exposure however some studies suggest a link between prenatal/ postnatal exposures and postnatal behavioral effects at ages 6 months and older. During pregnancy, Mn levels rise from 8 -10 µg/L to over 25 - 30 µg /L due physiological changes in the mother and fetal developmental requirements, the increase being attributed to the sequestration of dietary Mn. Mn from inhalation will contribute to maternal Mn levels however accounting for that in determining safe levels for both maternal and fetal effects is complicated by the multiple Mn exposure routes and dynamic Mn blood rise during

pregnancy. Personal protective equipment, workplace rules and implementation of a BEI for female welders may be more appropriate approaches to protecting female workers and the fetus from the effects of Mn than applying an uncertainty factor.

Recommendation:

Using the Roels (1992) study, different approaches can be used to estimate an OEL. A LOAEL can be derived from that study and appropriate uncertainty factors applied to implement a margin of safety. There was no NOAEL in that study so application of protective uncertainty factors is called for. Alternatively, benchmark dose modeling can be undertaken to extrapolate an exposure level for a low effect level (5%) to which uncertainty factors are applied for a further margin of safety. The LOAEL from Roels is 0.150 mg/m³ whereas BMD modeling results in a concentration of 0.077 mg/m³. Applying a cumulative uncertainty factor of 10 to both values results in an OEL range of 0.015 to 0.007 mg/m³ for respirable Mn.

A PEL of 0.01 R/ 0.1 T mg/m³ is proposed for Mn. A toxicokinetic uncertainty factor of 3 is applied due to the greater potential for pulmonary deposition/absorption of Mn fume. An intraspecies uncertainty factor of 3 is applied to address possible fetal effects. A PEL of 0.1 mg/m³ is proposed for total Mn based on an approximate 1/10 ratio of respirable/total fractions in non-welding processes. For welding fume, a PEL of 0.01 T mg/m³ is proposed since fume is in respirable range and the STEL of 3 mg/m³ is retained.

Usage information: EPA TSCA Chemical Data Reporting (CDR), EPA Toxics Release Inventories (TRI), other sources:

In 2015, there were 69 TSCA CDR records for manganese (usage in excess of 25,000 lbs) in U.S. Of these, 3 were in California. In 2016, there were 4008 TRI records for manganese of which 38 were in California.

Measurement/Implementation Feasibility:

	OSHA Methods (validated)	NIOSH Method (validated)
	ID 121 (Atomic Absorption)	7302 (ICP)
	ID 125G (ICP for welding fume)	
Estimated LOD/LOQ	0.002/0.02 (µg) *	0.02 µg/sample LOD
	0.061/0.2 (µg) *	

* Calculations are based on a 50-mL solution volume and equations listed in Section 6.7.1 of ID 125G. At an air concentration of the proposed respirable PEL, 190 µg Mn would be collected over an 8 hour period

Media	MCEF	MCEF
	PVC (welding fume)	

Measurement issues	restrict filter loading to < 2 mg total dust
	welding fume is measured inside the welding helmet

Based upon the recommended changes to the Mn PELs to 0.01mg/m³ respirable as welding fume and 0.1 mg/m³ total dust, there are no sampling or analytical feasibility issues.

Economic Impact Analysis/Assessment

The Division has made a determination that this proposal is not anticipated to result in a significant, statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. This proposal will not have any effect on the creation or elimination of California jobs nor result in the creation or elimination of existing businesses or affect the expansion of existing California businesses. The Division anticipates that any potential costs will be balanced by avoiding or minimizing the costs inherent in workers' compensation claims, lost work time, and productivity losses that would have been caused by exposure related illness of employees.

The PEL proposed is consistent with recent scientific findings, of which professional health and safety staff and consultants of these employers and others with significantly exposed employees should be aware. Many of these entities already seek to control employee exposures to chemicals to levels below existing PELs in the interest of business continuity and minimization of tort and workers compensation liability

Welding is the primary occupation in California with exposure to manganese. Welders are also exposed to other toxic metals with their own low PELs, such as chromium. An estimated 30,000+ California workers are employed as welders. Most California employers currently address respiratory hazards of welding via a combination of inexpensive local exhaust ventilation systems placed near the location of the welding work and by respiratory protection. Manganese exposure during the welding process is a result of the manganese content of both the base metal and the filler metals. Different welding processes result in differing levels of exposure to manganese. In many cases it is technologically and economically feasible to substitute a low manganese exposure welding process for a high-exposure welding process. Shielded Metal Arc Welding (SMAW) is the process creating the highest manganese exposures, but Gas Metal Arc Welding (GMAW or MIG) or Flux-cored Arc Welding (FCAW) generally are successful substitutes. In some cases, manganese welding fume emissions can be reduced by 80% by process substitution.

Setting a Permissible Exposure Limit for manganese that is up-to-date and consistent with current scientific information and state policies on risk assessment will send appropriate market signals to employers with respect to the costs of illness and injury, which chemicals can impose on workers and their families, the government, and society at large. With appropriate market signals, employers may be better able to choose work practices materials for use in the workplace that impose less of a burden on workers and society. There are no anticipated benefits to the state's environment.

The economic benefits from the proposed PEL will result primarily from reduced neurological effects among exposed workers.

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