

*CHRONIC TOXICITY SUMMARY*

## MANGANESE AND COMPOUNDS

<i>Molecular Formula</i>	<i>Synonyms</i>	<i>Molecular Weight</i>	<i>CAS Reg. No.</i>
Mn	elemental manganese; colloidal manganese; cutaval	54.94 g/mol	7439-96-5
MnO	manganese oxide; manganese monoxide; manganosite	70.94 g/mol	1344-43-0
MnO <sub>2</sub>	manganese dioxide; black manganese oxide	86.94 g/mol	1313-13-9
Mn <sub>3</sub> O <sub>4</sub>	manganese tetroxide; trimanganese tetraoxide; manganomanganic oxide	228.82 g/mol	1317-35-7
MnCl <sub>2</sub>	manganese chloride; manganese dichloride; manganous chloride	125.84 g/mol	7773-01-5

### I. Chronic Toxicity Summary

*Inhalation reference exposure level*

**0.2 µg/m<sup>3</sup>**

*Critical effect(s)*

Impairment of neurobehavioral function in humans

*Hazard index target(s)*

Nervous system

### II. Physical and Chemical Properties (HSDB, 1999)

*Description*

Lustrous, gray-pink metal (Mn); green (MnO), black (MnO<sub>2</sub>) or pink (MnCl<sub>2</sub>) crystals; brownish-black powder (Mn<sub>3</sub>O<sub>4</sub>)

*Molecular formula*

See above

*Molecular weight*

See above

*Density (in g/cm<sup>3</sup>)*

7.21-7.4 (Mn – depending on allotropic form); 5.43-5.46 (MnO); 4.88 (Mn<sub>3</sub>O<sub>4</sub>); 2.977 @ 25°C (MnCl<sub>2</sub>)

*Boiling point*

1962°C (Mn); not available (MnO); unknown (Mn<sub>3</sub>O<sub>4</sub>); 1190°C (MnCl<sub>2</sub>)

*Melting point*

1244 ± 3°C (Mn); 1650°C (MnO); 2847°C (Mn<sub>3</sub>O<sub>4</sub> - NIOSH Pocket Guide™, 1995); 650°C (MnCl<sub>2</sub>)

*Vapor pressure*

1 torr @ 1292°C (Mn); non-volatile at room temperature (Mn<sub>3</sub>O<sub>4</sub>); not available (MnO; MnCl<sub>2</sub>)

*Solubility*

Sol. in dil. acids and aq. solns. of Na- or K- bicarbonate (Mn); sol. in NH<sub>4</sub>Cl, insol. in H<sub>2</sub>O (MnO); insol. in H<sub>2</sub>O, HNO<sub>3</sub>, or cold H<sub>2</sub>SO<sub>4</sub> (MnO<sub>2</sub> - Reprotect®, 1995); insol. in H<sub>2</sub>O, sol. in HCl (Mn<sub>3</sub>O<sub>4</sub>); 72.3 g/100 ml H<sub>2</sub>O @ 25°C (MnCl<sub>2</sub>)

*Conversion factor*

Not applicable (dusts or powders)

### III. Major Uses or Sources

Metallic manganese is used in the manufacturing of steel, carbon steel, stainless steel, cast iron, and superalloys to increase hardness, stiffness, and strength (HSDB, 1995). Manganese chloride is used in dyeing, disinfecting, batteries, and as a paint drier and dietary supplement. Manganese oxide (MnO) is used in textile printing, ceramics, paints, colored glass, fertilizers, and as food additives. Manganese dioxide is used in batteries and may also be generated from the welding of manganese alloys. Manganese

tetroxide may be generated in situations where other oxides of manganese are heated in air (NIOSH Pocket Guide, 1995). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 126,107 pounds of manganese (CARB, 1999).

#### IV. Effects of Human Exposure

Male workers (n=92, plus 101 matched controls) in an alkaline battery plant in Belgium exposed to manganese dioxide were the subject of a cross-sectional epidemiological investigation (Roels *et al.*, 1992). Evaluation of the subjects included tests for neurobehavioral function, lung function, hematological parameters, and urinalysis. Exposed workers showed significant differences in performance on tests of visual reaction time, eye-hand coordination, and hand tremor. Occupational-lifetime integrated respiratory dust (IRD) levels ranged from 0.04-4.43 mg Mn/m<sup>3</sup>-yr with a geometric mean of 0.793 mg Mn/m<sup>3</sup>-yr. Average exposure time was 5.3 years, with a range of 0.2-17.7 years. The authors grouped the workers into three exposure groups based on the IRD levels: <0.6, 0.6-1.2, and >1.2 mg Mn/m<sup>3</sup>-yrs. Although there was an indication of a linear dose-related trend for visual reaction time and hand steadiness, the authors concluded that "analysis of the data on a group basis...does not permit us to identify a threshold effect level for airborne Mn." A daily average exposure level of 0.15 mg Mn/m<sup>3</sup> was derived by dividing the geometric mean of the IRD (0.793 mg Mn/m<sup>3</sup>-yr) by the average exposure time (5.3 yr).

In an earlier study, 141 male workers plus 104 matched control workers were examined for effects of exposure to MnO<sub>2</sub>, manganese tetroxide (Mn<sub>3</sub>O<sub>4</sub>), and other manganese salts (Roels *et al.*, 1987). Tests measuring visual reaction time, eye-hand coordination, hand tremor, and short-term memory were found to be significantly different in the manganese-exposed group. Statistically significant clinical symptoms (as evaluated in a questionnaire) included fatigue, tinnitus, finger trembling and irritability. Self-reported prevalence of coughs, colds and acute bronchitis were increased in the manganese exposed group relative to controls. Mean time of employment was 7.1 years, with a range of 1-19 years. Total airborne manganese dust levels had an arithmetic mean of 1.33 mg/m<sup>3</sup> and a geometric mean of 0.94 mg/m<sup>3</sup>.

Several other studies have identified neurobehavioral endpoints of manganese toxicity in human populations. A matched-pair cross-sectional study investigated 74 pairs of manganese alloy workers (Mergler *et al.*, 1994). Matched pairs were found to be discordant in reporting a number of adverse clinical symptoms including the following areas: fatigue, emotional state, memory, attention, concentration difficulty, nightmares, unusual sweating, sexual dysfunction, lower back pain, joint pain, and tinnitus. Motor function tests also revealed deficits in the manganese exposed group. Olfactory perception was enhanced in the manganese exposed group. Exposure levels were estimated at a geometric mean of 0.035 mg Mn/m<sup>3</sup> for respirable dust and 0.225 mg Mn/m<sup>3</sup> for total dust. Mean duration of exposure was 16.7 years.

Workers in two Swedish foundries were evaluated for potential neurobehavioral effects from exposure to manganese (Iregren, 1990). Exposure levels ranged from 0.02-1.4 mg Mn/m<sup>3</sup> with a mean of 0.25 mg Mn/m<sup>3</sup>. Simple reaction time, standard deviation of reaction time, finger-tapping speed, digit-span short term memory, speed of mental addition, and verbal understanding were significantly different from controls among manganese exposed workers.

Further reporting of the workers described by Iregren (1990) evaluated more neurobehavioral and electrophysiological endpoints of toxicity from manganese exposure (Wennberg *et al.*, 1991; Wennberg *et al.*, 1992). Although many of the parameters measured showed differences (increased self-reported health symptoms, increased abnormal EEGs, abnormal extrapyramidal function), these results were not statistically significant.

The workers reported on by Roels *et al.* (1987) were examined for potential reproductive toxicity (Lauwerys *et al.*, 1985). These investigators found that for workers divided into certain age groups (16-25 and 26-35), there was a decrease in the number of children born to these workers.

Evaluation of reproductive toxicity in the workers reported by Roels *et al.* (1992) showed no difference in the probability of live birth in a comparison of manganese exposed workers with controls (Gennart *et al.*, 1992). Comparison of reproductive hormones (FSH, LH, prolactin) also showed no differences between the groups.

Junior high school students exposed to manganese were examined for potential effects on the respiratory system (Nogawa *et al.*, 1973). Measurement of atmospheric manganese levels showed a 5-day average level of 0.0067 mg Mn/m<sup>3</sup> 300 m from the school.

## V. Effects of Animal Exposure

Toxic effects have been described in animals exposed to manganese compounds by inhalation (Shiotsuka, 1984; Suzuki *et al.*, 1978; Moore *et al.*, 1975). Shiotsuka *et al.* (1984) demonstrated increased incidence of pneumonia among rats exposed for 2 weeks to manganese dioxide concentrations ranging from 68-219 mg/m<sup>3</sup>. Monkeys exposed to manganese dioxide concentrations ranging from 0.7-3.0 mg/m<sup>3</sup> for 10 months showed increased incidence of pulmonary emphysema (Suzuki *et al.*, 1978). Hamsters and rats exposed for 56 days to 0.117 mg Mn<sub>3</sub>O<sub>4</sub>/m<sup>3</sup> showed bronchial lesions (Moore *et al.*, 1975).

High concentrations of manganese (>10 mg/m<sup>3</sup>) have decreased host resistance in exposed animals (Adkins *et al.*, 1980; Bergstrom, 1977; Maigetter *et al.*, 1976).

Nine month inhalation toxicity studies in rats and monkeys exposed to levels as high as 1.15 mg Mn<sub>3</sub>O<sub>4</sub>/m<sup>3</sup> produced no significant pulmonary effects (Ulrich *et al.*, 1979a; Ulrich *et al.*, 1979b; Ulrich *et al.*, 1979c). Monkeys and rats were continuously exposed over nine months to 11.6, 112.5, or 1152 µg Mn/m<sup>3</sup> as Mn<sub>3</sub>O<sub>4</sub> aerosol (aerodynamic diameter of approximately 0.11 µm) (Ulrich *et al.*, 1979a). Body weight gain was accelerated in rats exposed to the highest dose. Hemoglobin concentrations were slightly increased for both sexes and both species exposed to 1152 µg Mn/m<sup>3</sup>. No significant effects on organ weights or histopathologic findings were reported (Ulrich *et al.*, 1979b). No significant effects on pulmonary function, limb tremor, or electromyographic activity were noted (Ulrich *et al.*, 1979c).

Specific uptake of manganese through the olfactory mucosa to olfactory bulbs of the brain followed by widespread brain distribution has been reported (Tjalve *et al.*, 1996). This effect complicates the use of animal inhalation data in estimating human health effects.

## VI. Derivation of Chronic Reference Exposure Level

<i>Study</i>	Roels <i>et al.</i> , 1992
<i>Study population</i>	Occupationally-exposed humans
<i>Exposure method</i>	Discontinuous occupational inhalation exposure to manganese dioxide (0.2, 1.0, and 6.0 mg/m <sup>3</sup> )
<i>Critical effects</i>	Impairment of neurobehavioral function
<i>LOAEL</i>	0.15 mg respirable manganese dust/m <sup>3</sup> (geometric mean from exposures of 0.040 to 4.4 mg Mn/m <sup>3</sup> -years)
<i>NOAEL</i>	Not observed
<i>Study continuity</i>	8 hours per day, 5 days per week
<i>Average occupational exposure</i>	0.054 mg/m <sup>3</sup> for LOAEL group (based on an 8-hour TWA occupational exposure to 10 m <sup>3</sup> manganese contaminated air per day out of 20 m <sup>3</sup> total air inhaled per day over 5 days/week)
<i>Human equivalent concentration</i>	0.054 mg/m <sup>3</sup> for LOAEL group
<i>Study duration</i>	5.3 years (average; range = 0.2-17.7))
<i>LOAEL uncertainty factor</i>	10
<i>Subchronic uncertainty factor</i>	3
<i>Interspecies uncertainty factor</i>	1

<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	300
<i>Inhalation reference exposure level</i>	0.2 µg/m <sup>3</sup>

OEHHA used the same study on which USEPA based its RfC of 0.05 µg/m<sup>3</sup>. USEPA included a Modifying Factor (MF) of 3 for database deficiencies (lack of developmental data and potential differences in toxicity for different forms of manganese). The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

In the derivation of its reference concentration for manganese and compounds, the U.S. EPA selected the Roels *et al.* (1992) study for establishing the exposure level associated with adverse health effects. Although this study did not establish a no-observed-adverse-effect-level (NOAEL), clear evidence of toxicity was established at the level of exposure, which was found in the facility studied, and was therefore taken to be a LOAEL. This study offers several advantages over the other available studies of manganese toxicity. (1) The study population was human. (2) The workers were only exposed to a single manganese compound. (3) The study population was well controlled for with matching for age, height, weight, work schedule, coffee and alcohol consumption, and smoking. (4) The exposure duration was relatively long and work practice continuity suggests exposure levels changed little over time. (5) The effects observed were consistent with those observed among other workers occupationally exposed to manganese.

## **VII. Data Strengths and Limitations for Development of the REL**

The strengths of the inhalation REL for manganese include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating exposure and the potential variability in exposure concentration, the lack of chronic inhalation exposure studies, and the lack of reproductive and developmental toxicity studies.

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