MANGANESE, ELEMENTAL AND INORGANIC COMPOUNDS

CAS number: 7439-96-5 (Manganese)

Molecular formula: Mn

TLV–TWA, 0.02 mg/m^3, as Mn, Respirable particulate matter
0.1 mg/m^3, as Mn, Inhalable particulate matter

A4 — Not Classifiable as a Human Carcinogen

TLV® Recommendation

The respiratory tract is the most important portal of entry for manganese in the occupational setting. The inhalation toxicity of manganese is a function of particle dosimetry and subsequent pharmacokinetic events. Particles depositing in the upper respiratory tract and major intrathoracic airways (cleared mainly by mucociliary clearance) are swallowed into the gastrointestinal tract where absorption is quite low (about 3–5%). Some absorption of manganese occurs in the upper respiratory tract, notably via the olfactory nerve and possibly direct transport to the central nervous system (CNS) (Tjalve et al., 1995, 1996; Tjalve and Henriksson, 1999). Particles in the respirable size fraction are most likely to be taken up via the olfactory route, but uptake of manganese from larger soluble particles cannot be ruled out.

Clinical evidence of nervous system damage—*manganism*—has been observed in workers exposed to manganese or its inorganic compounds at levels below 5 mg Mn/m^3 (total dust). The World Health Organization (WHO) concluded that clinical disease occurs at manganese levels as low as 2–5 mg Mn/m^3 total dust (IPCS, 1981). Even more sensitive effects of manganese exposures occur in the CNS and can be detected by tests of neurological and neurobehavioral function. These effects occur at exposure levels considerably less than those associated with manganism, and some may persist after cessation of exposure.

In a cross-sectional study, Roels and coworkers (1992) found neurotoxic effects in Belgian workers and they suggested that an 8-hour TWA of 0.036 mg Mn/m^3 (respirable aerosol) would protect most workers from the CNS effects of manganese. It is possible to derive from these data the exposure levels for impaired hand steadiness affecting 5%, 2.5%, and 1% of individuals: these are 0.05, 0.02, and 0.007 mg Mn/m^3 (respirable aerosol), respectively. Further analysis of these data by the Agency for Toxic Substances and Disease Registry (ATSDR, 2000) using the benchmark dose (BMD) approach produced a $BMDL_{10}$ of 0.07 mg Mn/m^3 (respirable fraction) as a no-observed-adverse-effect-level.

Crump and Rousseau (1999) reported an additional 11 years of follow-up of workers from an earlier study of Roels et al. (1987b). In general, neurological test results obtained in an 11-year follow-up period were comparable or superior to results previously obtained by Roels et al. (1987b), despite the fact that the workers were older and had been exposed longer. The results of this study, while not conclusive, provided evidence that the sub-clinical effects of manganese reported earlier by Roels et al. (1987b) did not appear to be progressing with continued exposure.

Mergler and co-workers (1994) used a paired study design that individually matched exposed workers and controls. This detailed neurobehavioral study reported effects among workers exposed to a median level of 0.032 mg Mn/m^3 (respirable aerosol). The plant closed shortly after this study and workers were re-examined after a 14-year period of no exposure to manganese. Several manganese-related neurobehavioral changes were still observed in these workers and some of the persistence related to prior cumulative exposure to manganese (Bouchard et al., 2007a, b).

Lucchini et al. (1999) derived a lowest-observed-adverse-effect level (LOAEL) for exposure to manganese of approximately 0.10 mg Mn/m^3 (total dust). This LOAEL represented the average concentration of manganese that was associated with a neurobehavioral deficit after an average exposure period of 11.5 years. The effects noted in this study occurred at a geometric mean level corresponding to 0.038 mg Mn/m^3 (respirable aerosol).

Bast-Pettersen et al. (2004) showed increased tremor (impaired hand steadiness) in workers exposed to a geometric mean level of 0.036 mg Mn/m^3 (respirable aerosol).

In a large study of South African manganese smelter workers, Young and colleagues (2005) demonstrated increased neurobehavioral changes among workers exposed to 0.01–0.04 mg Mn/m^3 (respirable aerosol).

In arriving at a TLV for manganese, 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) among welders, 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 in 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 aerosol) would lead to impaired hand steadiness (detected with subtle tests but not clinically) in 2.5% of workers.

Virtually all manganese is absorbed from particles deposited in the fine, gas-exchanging regions of the lungs. Thus, the particles of greatest concern are in the fine respirable fraction (mostly < 4 μm).

Because some occupational exposure profiles include aerosols with a substantial fraction of particles larger than 4 μm MMAD, a supplementary TLV–TWA of 0.1 mg Mn/m^3, inhalable particulate matter, is also recommended for conditions where particles > 4 μm are anticipated. An inhalable aerosol limit provides some safeguard for intestinal absorption secondary to inhalation exposure, and possibly absorption from more soluble particles deposited in the nasopharynx. The ratio of inhalable to respirable mass may vary from 1:1 (as for most forms of welding) to 10:1 or higher (as in the ferroalloy industry) (Ellingsen et al., 2003b). We selected a midpoint ratio of 5:1, applied this to the recommended respirable exposure limit, and estimated the inhalable aerosol limit as 0.1 mg Mn/m^3. A ratio of 5:1 for inhalable to respirable concentrations of manganese is similar to that proposed by the U.K. Institute for Environment and Health (Levy et al., 2003). If an inhalable aerosol limit for manganese is used by the industrial hygienist, it should be *in addition to* the respirable aerosol limit.

Sufficient data were not available to recommend a TLV–STEL, or Skin, RSEN, or DSEN notations.

Owing to equivocal oral feeding studies in animals relating to carcinogenicity of manganese, the absence of manganese inhalation studies for cancer in animals, and the lack of human studies assessing manganese-related cancers, an A4, Not Classifiable as a Human Carcinogen, notation is assigned.

TLV® Basis

Central nervous system (CNS) impairment.

Chemical and Physical Properties

Elemental manganese, atomic number 25, in group VIIB of the periodic table, is a gray-white metal resembling iron, but is harder and more brittle. It is a highly reactive metal and exists in seven oxidation states. Its most important ore is the black oxide (MnO_2) known as *pyrolusite*. Chemical and physical properties of elemental manganese include (ATSDR, 2000; U.S. NLM, 2008):

- Molecular weight: 54.94, varies
- Specific gravity: 7.2–7.4, depending on allotropic form
- Melting point: 1244°C
- Boiling point: 2095°C
- Vapor pressure: 0.0075 torr at 955°C
- Flammable limits: flammable and moderately explosive in dust form when exposed to flame
- Solubility: soluble in dilute acids
- Conversion factor at 25°C: 1 mg/m^3 = 0.45 ppm

Ferromanganese fume, generated in the pouring and casting of molten ferromanganese metal alloy, contains largely manganese tetroxide (Mn_3O_4) as determined by X-ray diffraction analysis. The fume is formed when MnO_2 is heated strongly in air. Chemical and physical properties of manganese tetroxide include (ATSDR, 2000; U.S. NLM, 2008):

- Molecular weight: 228.79
- Melting point: 1564°C
- Solubility: insoluble in water; soluble in hydrogen chloride with evolution of chlorine
- Conversion factor at 25°C: 1 mg/m^3 = 0.11 ppm

Major Sources of Occupational Exposures

Manganese and its inorganic compounds are used widely in several industries. The most common forms are metallic Mn, and compounds where manganese exists in the Mn(II), Mn(III), and Mn(IV) forms (chiefly as $MnCl_2$, $MnSO_4$, $MnPO_4$, MnO_2, and Mn_2O_3). Manganese is especially noted for alloying with other metals and imparting hardness, such as in the manufacture of steel.

Inorganic compounds of manganese have a variety of other uses. Manganese chloride ($MnCl_2$) is used as a catalyst and as an animal feed supplement. Both MnO_2 and $MnCl_2$ are used in the production of dry-cell batteries. The oxide is also used in the manufacture of fireworks, matches, porcelain, and glass-bonding materials. Manganese sulfate ($MnSO_4$) is used in fertilizers, ceramics, glazes, and varnishes; as a nutritional supplement; and as a fungicide.

Airborne levels of manganese in mines have ranged from 1.5 to 450 mg Mn/m^3 (U.S. EPA, 1984); in ferroalloy foundries from 0.3 to 2.0 mg Mn/m^3 (Saric and Lucic-Palaic, 1977); in dry cell battery manufacture from 3 to 18 mg Mn/m^3 (Emara et al., 1971); in welding operations mostly from 1 to 4 mg Mn/m^3 (Sjögren et al., 1990), but as high as 14 mg Mn/m^3 when welding with Mn-containing wire (WHO, 1999). Mean concentration levels less than 1 mg Mn/m^3 have been found by other investigators in various work settings (Bast-Pettersen et al., 2004; Ellingsen et al., 2003b; Lucchini et al., 1995, 1999; Mergler et al., 1994; Roels et al., 1987a, b, 1992, 1999).

Deposition of inhaled manganese-containing particles in the respiratory tract of workers depends on the physical workload (tidal volume, breathing rate, nose or mouth breathing) and can vary considerably as a result of the manufacturing process. Oberdöerster and Cherian (1988) reported that airborne manganese particles can span a wide size range, from sub-micron to > 10 μm in diameter, whereas manganese fume (generated during melting, steel-making, or welding) is largely in the submicron range.

Size-selective exposure measurements among Mn-exposed workers are few (Bast-Pettersen et al., 2004; Ellingsen et al., 2003b; Hetland et al., 1997; Myers et al., 2003a, b; Young et al., 2005). For the most part, exposures have been reported either as "total dust" aerosol, using a closed-face 25- or 37-mm cassette, or as "respirable" aerosol. In manganese alloy operations, the traditional "total dust" sampler appears to underestimate exposure to inhalable aerosol by a factor of about two relative to the IOM Inhalable Sampler (Hetland et al., 1997). Bast-Pettersen and coworkers (2004) noted a geometric mean exposure of 0.30 mg Mn/m^3 inhalable particulate matter in Mn alloy production workers, of which 10.6% (or 0.03 mg Mn/m^3) was in the respirable size fraction, and data of Ellingsen and colleagues (2003b) showed inhalable to respirable ratios of 11.6:1 for arithmetic means, and 8.4:1 for geometric means in the same population.

Other studies of manganese alloy production workers have reported geometric mean total dust levels of 0.27 and 0.24 mg Mn/m^3 in furnace areas, and 0.12 and 0.055 mg Mn $/m^3$ in maintenance areas (Lucchini et al., 1995, 1997, 1999). A geometric mean concentration of 0.94 mg Mn/m^3 (total aerosol) was reported in a plant producing manganese oxides and salts (Roels et al., 1987a, b), and 0.05 mg Mn/m^3 (total aerosol) in a manganese ore processing plant (Chia et al., 1993). Individual exposures, averaged annually, in an Australian ferroalloy plant were 0.38 mg Mn/m^3 (inhalable aerosol) and 0.12 mg Mn/m^3 (respirable aerosol) (Summers et al., 2011).

Welding and other processes that generate metal fumes from manganese-containing alloys are a recognized source of exposure to fine manganese particles, and high concentrations of manganese oxide (MnO_2) can be present in the fume (Moreton, 1977). In addition, MnO_2 is used as a flux agent in the coatings of shielded arc electrodes and as an alloying element in electrodes (Villaume et al., 1979).

There were roughly 466,400 welders in the U.S. in 2008 (Bureau of Labor Statistics, 2010), and over one million worldwide who did welding as part of their job (Antonini, 2003). Since the early 1990s, concerns have increased about manganese exposure in welding fumes (Sjögren et al., 1990, 1996). Exposure arises from manganese content in the metals being welded, as well as manganese present in certain welding rods and wires. Korczynski (2000) found personal exposure levels of 0.01–4.93 mg Mn/m^3 "total aerosol" in 42 Canadian welders, and 62% had manganese exposures > 0.2 mg Mn/m^3. In confined space operations, Bowler et al. (2007) found personal exposures of 0.11–0.46 mg Mn/m^3 respirable aerosol. Particles in welding fume are generally less than 4 μm in diameter and, therefore, in the respirable size range.

Exposure chamber studies (Harris et al., 2005) have shown that levels from welding fumes inside a welding helmet can be consistently greater than 0.1 mg Mn/m^3 respirable aerosol—in some cases as high as 1.0 mg Mn/m^3—even when the general ventilation is greater than 2000 cfm. Area samples upstream and downstream from welding operations may regularly exceed 0.2 mg Mn/m^3 respirable aerosol, indicating hazards to other workers near welding operations (Harris et al., 2005).

Animal Studies

Manganese is an important cofactor for many enzymes (Michalke et al., 2007; WHO, 2004), particularly in the catalysis of electron transfer reactions (e.g., Mn superoxide dismutase). In biological systems, the oxidation states +II and +III predominate. Owing to their chemical similarity, Mn^{2+} can substitute for Mg^{2+} as a cofactor in enzymes, and to a lesser degree can substitute for Ca^{2+} and Fe^{2+} (Crowley et al., 2000; Schäfer, 2004).

Extensive literature exists on the effects of manganese in experimental animals. Most of these data have been summarized by the ATSDR (2000) and the U.S. Environmental Protection Agency (U.S. EPA, 1993).

A recent review (Gwiazda et al., 2007) looked at the adequacy and consistency of animal studies in the evaluation of the neurotoxic effects of chronic low-level manganese exposures in humans. The authors examined subchronic/chronic rodent and nonhuman primate studies to determine whether a consistent dose-response relationship existed, whether effects progressed with increasing dose, and whether the data were sufficient to evaluate effects of chronic low-level exposures in humans. Monkey studies produced pathologic changes that most closely resembled manganese-induced human pathology, with changes seen at low exposures in the globus pallidus, and at higher exposures in the caudate nucleus and putamen.

Because animal data have shown that toxicity of manganese at low exposure levels differs qualitatively from higher exposure levels, Gwiazda et al. (2007) concluded that animal data may be of limited relevance for risk assessment of chronic low-level manganese exposures in humans.

Chronic/Carcinogenicity

No studies were noted regarding carcinogenic effects in humans or animals from inhalation exposure to manganese. No studies were found concerning ingestion of manganese and cancer in humans.

Oral feeding and intraperitoneal instillation studies in animals have shown mixed results (Furst, 1978; Sunderman et al., 1974, 1976; Stoner et al., 1976; Witschi et al., 1981). Most reported negative findings, but one (Stoner et al., 1976) noted an increased incidence of pulmonary tumors at the highest dose administered by intraperitoneal injection.

The National Toxicology Program (NTP, 1993) reported on two-year feeding studies in rats and mice. No increased incidence of neoplasms was observed in male or female rats. Thyroid follicular dilatation and hyperplasia were significantly greater in male and female mice exposed to 15,000 ppm than in controls. It was concluded that there was equivocal evidence of carcinogenic activity of manganese (II) sulfate based on the marginally increased incidence of thyroid gland follicular cell adenoma and increased follicular cell hyperplasia.

Genotoxicity

Manganese (II) was not mutagenic in several *Salmonella typhimurium* strains, with or without exogenous metabolic activation (Valencia et al., 1985). Tests for induction of sister-chromatid exchange with Mn (II) were positive (Galloway et al., 1987).

Reproductive/Developmental Toxicity

Several studies of manganese administration to female rats on days 6–17 of gestation at various doses have not resulted in female reproductive toxicity (Grant et al., 1997; Kontur and Fechter, 1985). In a 2-year NTP study (NTP, 1993), no adverse reproductive effects from $MnSO_4$ were observed in rats exposed up to 232 mg Mn/kg/day or in mice exposed to doses as high as 731 mg Mn/kg/day.

Developmental toxicity in the brain and male reproductive organs has been noted in rat pups administered inorganic manganese compounds orally or intravenously at levels 100 to 1000+ times higher than airborne exposure levels in workers (Deskin et al., 1980, 1981; Laskey et al., 1982, 1985; Kristensson et al., 1986).

Absorption, Distribution, Metabolism, and Excretion

Manganese absorption occurs mainly in the pulmonary alveoli after inhalation or in the gastrointestinal tract after ingestion. Deposition in the nose also may lead to uptake via the olfactory nerve and direct transport to the CNS (Tjalve et al., 1995, 1996; Tjalve and Henriksson, 1999). Manganese is absorbed through the epithelium of the gastrointestinal and respiratory tracts. Gastrointestinal absorption is about 3–5% of ingested dose (ATSDR, 2000). Manganese metabolism in humans is rigorously controlled by homeostatic mechanisms that have an effect mainly on gastrointestinal absorption and excretion. Manganese absorbed via the gastrointestinal tract is sequestered in the liver. Manganese is mainly eliminated in the feces. Most is excreted via the biliary tract and likely undergoes enterohepatic circulation.

Manganese disposition *in vivo* is influenced by the intake and stores of iron (Fe) in the body. Both metals compete for the same binding protein in blood (transferrin) and other transport systems (divalent metal transporter) (Roth and Garrick, 2003). Anemic humans and iron-deficient rats have increased intestinal absorption of manganese. Among workers, the level of manganese in blood appears to be influenced by iron status, even at physiological iron levels (Ellingsen et al., 2003a). It is possible that an excess of Fe may inhibit uptake of Mn across the blood brain barrier.

For occupational exposures, the inhalation pathway is especially important where the absorption rate is close to 100% for fine dusts deposited in the alveoli (Beliles, 1994); larger particles depositing in proximal airways are carried towards the digestive tract by mucociliary clearance (ATSDR, 2000). Morrow (1970) determined a half-life of about 66 days in humans after inhalation of sub-micronic particles of $^{54}MnO_2$.

Human Studies

Manganese has been shown to be an essential element in the nutrition of humans and for many animal species. It is involved in the formation of connective tissue and bone, in carbohydrate and lipid metabolism, and as a catalyst in several metabolic pathways (Wedler, 1994). There are no well-defined symptoms of manganese deficiency for humans.

Several reviews of the adverse effects of manganese in humans have been published (e.g., ATSDR, 2000; Clewell et al., 2003; Oliguy et al., 2003). A severe form of chronic manganese poisoning *(manganism)* primarily affects the CNS. Involvement of the extrapyramidal motor system leads to a disorder that clinically resembles Parkinson's Disease (PD).

Because manganese is a paramagnetic element, magnetic resonance imaging (MRI) can identify where manganese accumulates in the brain (Fitsanakis et al., 2006). In humans, manganese preferentially accumulates in the globus pallidus, followed by the substantia nigra *pars reticularis*, the corpus striatum, pineal gland, olfactory bulb, and substantia nigra *pars compacta*. This contrasts with PD, where the substantia nigra *pars compacta* is the first site to degenerate. Also, manganism involves impairment in GABA-related pathways, whereas PD does not. Manganism may be associated with some effect on dopamine pathways but does not respond to treatment with L-dopa, whereas PD shows severe impairment of dopamine metabolism and improves with administration of L-dopa (Cerosismo and Koller, 2006; Roth and Garrick, 2003). Manganese-induced neurological damage can persist and progress for many years after exposure to manganese ceases, even after blood and tissue levels appear to have returned to normal (Huang et al., 1993, 1998).

Manganism has been described since the 19th century. Fairhall and Neal (1943) collated reports from 12 countries of 353 cases of manganese poisoning between 1837 and 1940. According to Hunter (1975), at least 118 more cases had been reported by 1968. Early symptoms include languor, sleepiness, and weakness in the legs (Fairhall, 1957). A stolid, mask-like facial appearance, emotional disturbances (such as uncontrollable laughter), a spastic gait (called a "cock-walk"), and a tendency to fall backwards when lightly pushed are found in advanced cases (Fairhall and Neal, 1943; Flinn et al., 1940). In addition, a high incidence of pneumonia has been found in workers who have inhaled high levels of dusts and fumes of manganese or its compounds (Lloyd Davies, 1946).

The levels of airborne manganese were usually very high in mines and industries where clinical cases developed. Rodier (1955) noted manganese concentrations of 100–900 mg/m^3, and felt that values < 100 mg/m^3 would be reasonably safe. Flinn and co-workers (1940) reported manganese concentrations up to 170 mg/m^3, averaging 47 mg/m^3, in a mill where 11/34 (32%) workers were found to suffer from overt manganese poisoning. No cases occurred among workers exposed to less than 30 mg/m^3. However, studies in another ore mill with dusty operations, where workers performed similar tasks with more modern equipment and local exhaust ventilation, revealed manganese concentrations averaging 2.3 mg/m^3, with 6 mg/m^3 in the dustiest operation.

Lloyd Davies (1946) found that an average manganese concentration of 210 mg/m^3 was associated with pneumonia. Kesic and Hausler (1954) reported cases of manganese poisoning in a Yugoslavian plant where concentrations of MnO_2 dust were 7–63 mg/m^3; however, the rate of intoxication was low when concentrations were 3–9 mg/m^3. In contrast, Schuler and co-workers (1957) found chronic manganese poisoning in miners when only one-third of the air samples were above 5 mg/m^3.

Tanaka and Lieben (1969) recorded seven definite and 15 borderline cases of manganism in 75 Pennsylvania plants where 144 workers were exposed to manganese dust or fume levels exceeding 5 mg/m^3. Of the seven definite cases, four resulted from exposure to manganese dust and three from manganese fumes. No cases were reported in 48 workers exposed to air concentrations of fume or aerosol less than 5 mg/m^3.

Whitlock and co-workers (1966) reported two cases of manganese fume poisoning in a manganese steel plant where air sampling showed concentrations of 2.7–4.7 mg/m^3. However, Whitman and Brandt (1966) considered their air analysis data to be inadequate, and found no evidence of manganese poisoning at a time-weighted average concentration of roughly 5 mg/m^3.

In a study of a Pennsylvania steel plant (1957–1965), Smyth and co-workers (1973) reported that 5/71 (7%) workers had chronic manganism. Three of the five cases resulted from exposure to ferromanganese fumes, while the balance was from exposure to larger ferromanganese particles. Two of the three workers exposed to fumes had worked in the pig-casting operation as pourers for a period of five years where their average exposure was estimated to be 13.3 mg/m^3. The third individual worked in an area where he was exposed to fumes from a pouring operation in which the manganese air concentrations were less than 1 mg/m^3. The other two affected employees worked in a ferromanganese crushing and screening operation where air concentrations were roughly 30–50 mg/m^3.

In an effort to better understand the development of manganism, and its pre-clinical antecedents, researchers have focused on various tests of neurological and neurobehavioral function. Exposure-response relationships have been developed for a number of these tests.

Neurological/Neuropsychological Studies

Roels and colleagues (1987a, b) conducted a cross-sectional epidemiological study among 141 male workers exposed to manganese oxides and salts from manganese ore. The mean age of the workers was 34.3 years. The duration of employment ranged from 1–19 years, with a mean of 7.1 years. Roels et al. (1987a) reported on the effects of manganese on the lung, CNS, and some biological indices. The results were compared with a matched control group of 104 workers. The TWA concentration of airborne manganese dust (personal samples) ranged from 0.07 to 8.61 mg Mn/m^3, total aerosol (with an overall mean and median of 1.33 and 0.97 mg Mn/m^3, respectively). The particle size distribution and purity of the dust were not reported.

In reporting the results of respiratory effects, Roels and co-workers (1987b) found a significantly higher prevalence of cough in cold seasons, dyspnea during exercise, and recent episodes of acute bronchitis in the manganese-exposed group. With respect to lung function, mean peak expiratory flow, forced vital capacity, and forced expiratory volume in 1 second were each mildly decreased among smokers in the manganese exposed group relative to the unexposed workers. The magnitude and prevalence of these effects were unrelated to manganese levels in blood or urine, or to the duration of exposure. The authors observed no synergistic effect between manganese exposures and smoking for any of the lung function parameters.

To detect early effects of manganese on the CNS, Roels and colleagues (1987b) used a questionnaire, performed a standardized neurological examination, and conducted several psychomotor tests (hand tremor, short-term memory, and simple reaction time). The standardized neurological examination revealed a difference for rigidity of the trunk between control and manganese-exposed workers. Psychomotor tests showed that manganese-exposed workers exhibited a significantly longer mean reaction time, performed significantly less well in audio-verbal short-term memory tests, and differed significantly from the control group for eye-hand coordination and hand-steadiness parameters. This study indicated that a TWA exposure of 0.96 mg Mn/m^3 (total aerosol) led to adverse clinical effects in the CNS and lungs of some workers exposed for less than 20 years.

Roels and co-workers (1992) conducted a second cross-sectional epidemiological study among 102 male workers exposed to MnO_2 in a dry alkaline battery factory in order to assess the validity of the conclusions drawn in their first study (Roels et al., 1987a, b), and to better define an exposure limit for inorganic manganese compounds. The mean age of the workers was 31.3 years, and the duration of exposure was 5.3 years (range: 0.2–17.7 years). Results were compared with a matched control group of 104 workers of mean age 29.3 years. The median current airborne manganese concentrations, as determined by personal sample monitoring, were 0.71 mg Mn/m^3 (total aerosol) and 0.18 mg Mn/m^3 (respirable fraction). Data on particle size or purity were not presented, but the median cut-point for the respirable fraction was 5 µm. Total and respirable dust concentrations were highly correlated (R^2 = 0.81), with the manganese content of the respirable fraction being, on average, 25% of the total aerosol.

Occupational lifetime-integrated exposure to manganese was estimated for each worker by multiplying the current airborne manganese concentration for the worker's job classification by the number of years for which that classification was held, and adding the resulting (arithmetic) products for each job position a worker had held. The geometric mean of occupational-lifetime integrated respirable aerosol concentration was 0.79 mg Mn/m^3-year (range: 0.04–4.44 mg Mn/m^3-year), with a geometric SD of 2.91 mg Mn/m^3-year. The geometric mean occupational lifetime integrated total aerosol concentration was 3.51 mg Mn/m^3-year (range: 0.19–27.5 mg Mn/m^3-year).

On a group basis, the concentrations of manganese in blood (MnB) and urine (MnU) were significantly higher in the manganese-exposed group compared with controls. However, on an individual basis, no statistically significant correlation was found between MnB or MnU and various exposure parameters, such as duration of exposure, and current or integrated exposure to manganese. This finding was consistent with earlier work by Roels et al. (1987a, b).

A self-administered questionnaire on respiratory symptoms was used and analyzed separately for smokers, nonsmokers, and both groups combined. The analysis did not show any statistical difference between the control and manganese-exposed group in the prevalence of respiratory symptoms.

Analysis of a questionnaire on neurological complaints did not show any significant difference in the prevalence of reported symptoms between the controls and manganese-exposed groups. However, the manganese workers performed several neurofunctional tests and measurements less satisfactorily than did the control workers. The manganese workers had a significantly longer reaction time than the control group throughout the testing period. The results of five eye-hand coordination parameters were more erratic in the manganese-exposed workers than in the control subjects, and the results of the hole tremormeter test (hand steadiness) showed a systematic tendency towards higher mean tremor scores in the manganese group compared with the controls. Although the manganese-exposed workers performed less well in the audio-verbal short-term memory test than the controls, the mean scores of correctly recalled or recognized words were not significantly different between the groups.

The authors used a logistic regression model to analyze the data and found that hand tremor (hand steadiness) was the most sensitive measurement to define a threshold effect level (Roels et al., 1992). The data indicated that a lifetime integrated exposure to total manganese dust (LITD) above 3.58 mg Mn/m^3-year, or lifetime integrated exposure to respirable manganese dust (LIRD) above 0.73 mg Mn/m^3-year (equivalent to an average exposure of 0.036 mg Mn/m^3 for 20 years) could lead to an increased risk of tremor. Looked at differently, the logistic model for the probability (*p*) of abnormal hand steadiness showed a relationship with LIRD as follows:

$$ln\ [p/(1-p)] = 1.8615 \times log_{10}\ [LIRD] - 7.5197,$$

Substituting a value for *p* of 0.05 yields a value for LIRD of 0.287 mg Mn/m^3-year. After allowing for the average duration of exposure (5.3 years) among manganese workers, the predicted exposure level that would produce an abnormality in hand steadiness for 5% of workers would be 0.054 mg Mn/m^3, respirable particulate matter. For *p* values of 0.025 and 0.01, the corresponding predicted air levels of manganese would be 0.022 and 0.007 mg Mn/m^3, respirable particulate matter, respectively.

At an international symposium on manganese toxicity, Roels and Lauwerys (1992) recommended that the 8-hour TWA airborne concentration of manganese should not exceed 0.090 mg Mn/m^3 total dust, or 0.018 mg Mn/m^3 respirable dust for a working lifetime of 40 years in order to protect the majority (95%) of the exposed workers from the neurotoxicity of manganese.

As a follow-up to the cross-sectional study, Roels et al. (1999) conducted an eight-year longitudinal investigation of the same cohort in order to determine whether early effects on eye-hand coordination, hand steadiness, and simple visual reaction time were reversible. During the observation period, 1988–1995, monthly total dust samples were collected for manganese, producing more than 1300 personal air samples. Total dust measurements were obtained with cyclone samplers (SIMPEDS), and were calculated by summing the mass of dust penetrating the cyclone and the mass of dust collected in the cyclone. Roels et al. (1999) cautioned that the values reported as total airborne manganese did not conform to the standard definition of "total dust." Measurements with the SIMPEDS sampler met the respirable response curve recommended by the British Medical Research Council when sampling at a flow rate of 1.9–2.0 L/min. Unfortunately, Roels' group obtained measurements with a flow rate of only 1.5 L/min, leading to significant overestimation of the mass sampled.*

The MnO_2 aerosol exposures over the years showed a steady reduction in the annual geometric means of manganese concentration. Time trend analysis indicated a significant decline of manganese exposures in 1987–1995, with a more pronounced decrease after 1991–1992. The overall decrease in total aerosol concentration was from 0.80 mg Mn/m^3 in 1987 to 0.25 mg Mn/m^3 in 1995. Roels and co-workers (1999) concluded from the results of their prospective study that:

1. *The standardized application of the Eye-Hand-Coordination (EHC), Hand Steadiness (HST), and Simple Visual Reaction Time (VRT) tests was characterized by an excellent reliability, which is a prerequisite for a sound assessment of subclinical toxic effects of manganese on neurobehavioral functioning in the context of a longitudinal study design.*
2. *The 1987–1995 longitudinal study revealed that the severity of past chronic MnO_2 exposure determined the relative importance of the baseline deficit (10 to 30% on average) as to the precision of the hand-forearm movement and also the subsequent pattern of improvement when exposure declined. In the most exposed subgroups (medium and high), the deficit was only partially reversible after manganese exposure had dropped substantially with time; whereas in the low exposure subgroup, a complete normalization of the EHC test results was reached at the end of the study when the average MnT had dropped to about 30 percent of the initial levels. This finding was solely explained by the reduction of airborne MnO_2 particulate over time; a "healthy-worker-effect" mechanism is unlikely to have confounded the longitudinal findings. The temporal evolution of the HST and VRT test results, however, showed absence of improvement suggesting a rather irreversible situation.*
3. *A retest of control workers, 10 years after their first examination in 1987, demonstrated that age was not a confounding factor as to the EHC, HST, and VRT test results obtained in the present study.*
4. *The follow-up study in a group of ex-manganese workers corroborated the findings of the longitudinal study as to the temporal evolution of the EHC, HST, and VRT test results. Indeed, a significant improvement of the EHC performance was evidenced, whereas the HST and VRT results did not differ significantly between the last examination before exposure ceased and the follow-up examination after at least three years with virtually no MnO_2 exposure.*
5. *This study demonstrated also that pre-clinical impairment of the EHC performance (a potential precursor of clinical manganism) is detectable at an early stage and that only in rather low occupational manganese exposure conditions impairment of eye-hand coordination is likely to show a substantial improvement when manganese exposure is abated. Hence, adequate steps can be taken to prevent occupational manganism.*

Iregren (1990) evaluated workers exposed to manganese in two Swedish foundries (15 from each plant). Exposures varied from 0.02–1.40 mg Mn/m^3 total dust (mean 0.25 mg Mn/m^3; median 0.14 mg Mn/m^3) for periods of 1–35 years (mean 9.9 years). Air exposure measurements in each plant suggested that exposures had not changed in either facility for the preceding 18 years.

Each exposed worker was matched for age, geographical area, and type of work to two workers from other industries where manganese was not present. Significant differences were found between exposed and control groups for simple visual reaction time, the standard deviation of reaction time, and finger-tapping speed of the dominant hand.

In addition, mental addition speed, digit-span short-term memory, and vocabulary understanding differed significantly between exposed and control groups. The difference in vocabulary understanding suggested that the groups were not well-matched for general cognitive abilities. Nevertheless, with verbal performance used as an additional matching criterion, between-group differences remained statistically significant for simple reaction time, the standard deviation of reaction time, and finger-tapping speed. Further analyses using verbal test scores as a covariate also showed that the same three measures of neurobehavioral function differed between exposed and control workers. No significant correlation with exposure parameters was found within the exposed group to establish a dose-response relationship.

Wennberg and colleagues (1991, 1992) reported additional neurobehavioral and electrophysiological evaluations in these same workers. Increased rates of self-reported health symptoms, abnormal electroencephalograms, slower brain-stem auditory evoked

* Clewell et al. (2003) commented on this problem, and cited an unpublished analysis of Howard Cohen (letter dated April 29, 1999) suggesting that respirable fraction exposures reported by Roels et al. (1999) *should be reduced by 43%.*

potential latencies, and slower diadochokinesis[‡] were found in exposed workers. Owing to small sample sizes, however, no significant differences were found between manganese exposed workers and their referents.

Mergler and colleagues (1994) reported results for 74 manganese-exposed workers and matched-pair controls employed in production of silicomanganese alloy. The geometric mean exposure concentrations using area samplers were 0.035 mg Mn/m^3, respirable aerosol (range: 0.001–1.27 mg Mn/m^3) and 0.225 mg Mn/m^3 total dust (range: 0.014–11.48 mg Mn/m^3). Discordant pairs, in which workers reported undesirable symptoms on a self-administered questionnaire but their matched pairs did not, were statistically significant for 33 of 46 items: fatigue; emotional state; memory, attention, and concentration difficulties; nightmares; sweating in the absence of physical exertion; sexual dysfunction; lower back pain; joint pain; and tinnitus. Signs typical of advanced manganese poisoning (e.g., hand tremor, changes in handwriting, loss of balance when turning, difficulty in reaching a fixed point) were similar among the manganese workers and referents, suggesting that the reported symptoms were probably not due to bias on the part of the manganese workers.

Greatest differences in neurobehavioral function were present in tests requiring coordinated alternating movements (diadochokinesis) or rapid movements. Workers performed significantly worse on the motor scale of a neuropsychological test battery, as well as on tests of hand steadiness, parallel-line drawing performance, and their ability to rapidly identify and mark specified alphabet characters within strings of letters. The manganese alloy workers differed also from matched controls on measures of cognitive flexibility and emotional state, and olfactory perception was also enhanced.

Overall, the results of neurobehavioral tests showed that manganese alloy workers differed from referents with respect to symptom reporting, emotional state, specific motor functions, hand steadiness, olfactory perception, and cognitive flexibility. Using the respective geometric means from this study, the U.S. EPA (1993) derived a LOAEL of 0.035 mg Mn/m^3 (respirable aerosol).

The plant where Mergler et al. (1994) studied manganese workers closed in 1990, shortly after the study, and these workers were re-evaluated in 2004 (Bouchard et al., 2007a, b). Of the surviving workers, 78% of the manganese-exposed group and 67% of referents were examined again. Persistent abnormalities were noted among the former manganese exposed group for several tests, especially in relation to neuromotor function (Luria Motor Scale) and in certain moods (anger/hostility, confusion/bewilderment), while tests of cognition that had been different between workers and referents appeared to show improvement over time (Bouchard et al., 2007b).

Neuropsychiatric changes in the surviving workers were examined in more detail (Bouchard et al., 2007a). Former manganese workers had persistently higher mean scores for depression and anxiety than referents. When cumulative manganese exposure was classified by tertiles and compared with referents, exposure-response relationships were noted for symptoms of depression, anxiety, hostility and somatization. These data indicate that manganese exposure is associated with a range of neurobehavioral and neuropsychiatric changes, some of which may persist for long periods after occupational exposure ceases.

Lucchini and colleagues (1995) reported findings among a group of 58 workers in a ferroalloy plant where total dust exposure levels had decreased from 0.07–1.59 mg Mn/m^3 to 0.03–0.27 mg Mn/m^3 in the 10 years before the study. The workers were examined during a temporary lay-off period ranging 1–42 days after cessation of exposure. Tests of simple reaction time, finger tapping, digit span, additions, symbol digit tests, comparison of shapes, and a vocabulary test were administered. Blood and urine manganese levels were measured, and a cumulative exposure index (CEI) was determined from job histories and measurements of total dust in the work sites. After log transformations, blood manganese levels were correlated with CEI estimates (R^2 = 0.36) and urinary levels (R^2 = 0.23), and urinary levels were correlated with CEI (R^2 = 0.16). The blood and urinary manganese levels were examined in regard to the time since last exposure, and the respective correlations were not affected by the duration of lay off.

Three exposure groups were defined: a high-exposure group (19 furnace workers) had current geometric mean exposures of 0.124 mg Mn/m^3-year (total dust), a geometric mean CEI of 0.668 mg Mn/m^3-year and a mean exposure duration of 13.8 years (mean exposure intensity: 0.048 mg Mn/m^3); a medium-exposure group (19 maintenance workers) had current geometric mean exposures of 0.070 mg Mn/m^3-year (total dust), with a geometric mean CEI of 0.199 mg Mn/m^3-year and a mean exposure duration of 11.8 years (mean exposure intensity: 0.017 mg Mn/m^3); and a low-exposure group (20 clerks, foremen, technicians) had current geometric mean exposures of 0.027 mg Mn/m^3-year (total dust), with a geometric mean CEI of 0.177 mg Mn/m^3-year and a mean exposure duration of 13.7 years (mean exposure intensity: 0.014 mg Mn/m^3). Significant manganese-related effects were noted for each of the neurobehavioral tests, with blood manganese

[‡] Diadochokinesis refers to performance of rapidly alternating, opposing movements (e.g., supination-pronation of the forearm) and is an indicator of extrapyramidal motor function. Slower diadochokinesis (dysdiadochokinesis) indicates impaired extrapyramidal pathways.

level being most highly correlated with abnormal tests. This study examined neurobehavioral function at manganese exposure levels among the lowest studied to date. Unfortunately, respirable aerosol levels were not obtained.

Lucchini and co-workers (1999) also reported data for 61 ferroalloy workers and 87 controls from a nearby hospital. They used questionnaires, a neurobehavioral test battery, and the Profile of Mood States (POMS). Personal and area samples for total dust were obtained. Average (geometric mean) manganese concentrations for total dust changed in different areas between 1981–1997: in the furnace room, the average dropped from 1.60 mg Mn/m^3 in 1981 to 0.24 mg/m^3 in 1997; in the casting area, the average increased from 0.15 to 0.26 mg Mn/m^3; and for welding operations, the average decreased from 0.17 to 0.055 mg Mn/m^3. A CEI was calculated for each worker. A positive correlation was observed between manganese concentrations in total dust and blood manganese (N = 55; R^2 = 0.13; P = 0.007), but no association was noted between CEI and manganese levels in blood or urine.

Higher symptom rates were observed in the alloy workers with respect to irritability, loss of equilibrium and rigidity. Tremor parameters, including the central frequency and its dispersion, were statistically different in the exposed workers relative to controls. Motor functions reflecting coordination of rapid and alternating movements and memory functions were impaired in the manganese-exposed workers. Dose-effect relationships were observed between the CEI and some of the test results. Following a conventional LOAEL-based approach for estimation of a safe exposure level, the authors used the geometric mean total dust CEI of the middle exposure subgroup (1.11 mg Mn/m^3-year) divided by the geometric mean exposure period (11.51 years) of that subgroup, to obtain an average exposure value of 0.097 mg Mn/m^3 total dust. Respirable aerosol levels averaged 2.6 times less than total dust measurements in this work setting. Dividing the total dust level of 0.097 mg Mn/m^3 by 2.6 yields a value of 0.038 mg Mn/m^3 (respirable particles) as the equivalent LOAEL exposure level.

Gibbs and co-workers (1999) reported on the medical surveillance of 75 U.S. workers with recent or historical exposure to manganese at a metal producing plant in northern Mississippi. Exposed workers were closely matched with 75 control workers who had no known history of occupational exposure to manganese. The two plants shared common medical, safety, and industrial hygiene services.

Airborne manganese levels were assessed for each of 12 job categories at the facility by collecting 63 side-by-side full-shift personal samples of total and respirable dust. Current workplace exposures averaged 0.066 mg Mn/m^3 respirable aerosol (median 0.051 mg Mn/m^3) and 0.180 mg Mn/m^3 total aerosol (median 0.086 mg Mn/m^3). Major equipment and work practice changes over the past several years were assessed, and the resultant effects on exposure were estimated. Based on this information, the total average cumulative lifetime exposure to respirable manganese among the 75 exposed workers was estimated to be 1.04 mg Mn/m^3-year.

Both manganese-exposed and control workers were assessed with tests of hand-eye coordination, hand steadiness, complex reaction time, and rapidity of finger tapping. A questionnaire was used to evaluate the workers' neuropsychological statuses. Performance decreased significantly with increasing age in tests of hand-eye coordination, complex reaction time, and finger tapping speed. No effect of manganese exposure was apparent in symptoms of depression, anxiety, fatigue, sleep disturbance, concentration, memory, mood changes, mania, tremor, or imbalance. This was a negative study among workers exposed currently to median levels of 0.05 mg Mn/m^3 (respirable aerosol) and who had low cumulative Mn exposures.

Crump and Rousseau (1999) reported on an additional 11 years of follow-up of workers at the manganese oxide- and salt-producing plant in Belgium that had been studied by Roels and coworkers (1987a, b). Between 1985 and 1996, workers at the manganese plant were tested routinely using the same battery of neurological tests and biological sampling that had been used by Roels' group (1987a, b). During this period of follow-up, blood and urine manganese levels were comparable to those measured during Roels' earlier studies. Overall, follow-up neurological test results were comparable or superior to results obtained earlier by Roels, despite the fact that the workers were older and had been exposed longer. However, tests of whether neurological scores of individual workers within the follow-up cohort decreased with continued occupational manganese exposure were hampered by the lack of an unexposed comparison group and were, therefore, inconclusive. In addition, major year-to-year differences in test results were observed that could not be explained by differences in age or manganese exposure, raising a concern regarding reproducibility of the test methods.

There was evidence that older workers performed significantly worse than younger workers on all of the tests, but particularly on tests of short-term memory and hand-eye coordination. A significant association was found between blood manganese and hand steadiness, but not between blood or urine manganese and other neurological tests. These findings are consistent with those reported previously by Roels, except that Roels found a relationship between blood manganese and hand-eye coordination. Thus, the results of the follow-up study, while inconclusive, provided evidence that the subclinical effects of manganese reported by Roels' group did not progress with continued exposure.

Myers and co-workers (2003a, b) conducted a large survey in South Africa of 589 production workers at manganese smelting works and compared them with 67 unexposed referents from an electrical assembly plant. Exposure estimates were based on 310 personal aerosol samples obtained with IOM inhalable dust samplers (Myers et al., 2003b), and the filters analyzed for manganese. A CEI was constructed for each worker. Average exposure intensity (INT) was obtained by dividing an individual's CEI by the number of years worked in the industry.

Average CEI was 16.0 ± 22.4 (SD) mg Mn/m^3-year inhalable fraction and INT averaged 0.82 ± 1.04 mg/m^3 inhalable fraction in the smelter workers. The referents had no detected manganese in their workplaces, were younger on average (38.6 versus 45.1 years) and had more years of schooling (8.0 versus 4.2 years) than the smelter workers. Significant differences between smelter workers and the external referents were noted for tests of motor performance (Santa Ana), visual retention (Benton), digit span and digit symbol (Myers et al., 2003a). The digit span and digit symbol tests also showed significant trends with increasing CEI levels. Tapping with the dominant and nondominant hands showed differences between smelter workers and unexposed referents, but only a marginally significant relationship with CEI. Mean visual reaction time did not differ significantly between the exposed and unexposed groups.

The use of CEI measurements rather than INT meant that actual exposure levels could not be assessed directly. This may have explained why some exposure-response relationships showed tendencies to decrease in effect with higher CEI. This could have reflected long-term exposures to relatively low levels, but another reason for inverted relationships might have been a form of selection bias whereby affected individuals migrated away from high exposure areas to low exposure areas, or had left the workforce with the least affected remaining. For whatever reason, the use of CEI (inhalable fraction) showed increasing exposure-response relationships only for digit span and digit symbol, with equivocal findings for tapping with the dominant and the nondominant hand.

Young and colleagues (2005) reported findings in the same South African smelter workers based on 98 personal respirable particle samples. Job exposure matrices were developed to assign individual respirable particulate exposures to manganese. Not all cells in the matrix had measured data, and missing data were estimated in two ways. Ratios of inhalable to respirable mass were obtained for cells that had both measurements, and such ratios were used to attribute exposures in cells that had only inhalable measurements. If neither measurement was available for a particular cell, the respirable exposure levels were interpolated based on exposures in similar activities elsewhere in the plant.

Mean CEI was 0.92 mg/m^3-year respirable fraction, and INT averaged 0.058 mg/m^3 respirable fraction (range: 0.003–0.51 mg Mn/m^3). When examining the exposure-response relationships, multiple linear and logistic models were used, with adjustments for age, years of schooling, past job exposures to neurotoxins, previous head injury, and home language.

Clearer exposure-response relationships were apparent using the INT for the respirable aerosol fraction (Table 1). It appears that some tests were more sensitive in detecting possible manganese-related effects: digit span, digit symbol score, and tapping with the dominant or nondominant hand showed increasing effects with increasing exposure levels. Testing for trends across exposure categories for these measurements was highly significant ($P <$ 0.01 in each case). Relative to an unexposed control group, the LOAEL for these sensitive indicators of effect appeared to lie in the range 0.01–0.04 mg Mn/m^3 respirable aerosol. Young and colleagues (2005) felt that the respirable aerosol measurements did not offer a better exposure estimate than the inhalable aerosol data. However, comparison of the inhalable aerosol results expressed as CEI (Myers et al., 2003b) with the respirable aerosol data expressed as INT (Young et al., 2005) shows that the latter provided a number of exposure-response findings that were more significant and consistent (Table 1).

The South African data also indicated that, in manganese smelting operations, particles > 4 μm contributed the major fraction of inhalable particulate mass, and for that reason a TLV–TWA for both respirable and inhalable fractions would be prudent.

Bast-Pettersen and coworkers (2004) examined 100 male manganese alloy production workers and 100 age-matched referents. They used a neurobehavioral test battery and exposure was assessed from airborne measurements, as well as blood and urine tests for manganese. The geometric mean exposure was 0.301 mg Mn/m^3 (inhalable particulate matter) or 0.036 mg Mn/m^3 (respirable particulate matter). Workers exposed to manganese differed significantly from referents with respect to increased tremor, but not in tests of cognitive speed/visual scanning, attention/short-term memory, or with respect to symptoms of sleep disturbance, fatigue, memory/concentration, emotional lability, somatic complaints, sensory or motor changes. This study indicated manganese-related effects on tremor at a geometric mean exposure of 0.036 mg Mn/m^3 respirable particulate fraction.

A group of 92 Danish steel workers were studied in 1989 and 1995, and 60 were re-examined in 2003 (Blond et al., 2007; Blond and Netterstrom, 2007). Cognitive and neuromotor function assessments were obtained on each occasion and compared with blood manganese and lead levels. Results of these studies are difficult to interpret in terms of exposure-response relationships for manganese. Air exposure

TABLE 1. Exposure-Response Findings Among South African Smelters in Relation to Average Manganese Exposure Intensity (INT), Expressed as Respirable Particulate Matter (mg Mn/m^3)

		Digit Span	Digit Symbol	Santa Ana	Mean Reaction Time (ms)	Tapping (dominant hand)	Tapping (other hand)	Endur-ance
Unexposed Referents, mean score		15.6	33.8	49.4	266.4	59.4	54.6	337.1
Exposed versus Referents		-2.1 §	-2.1 †	-4.3 §	10.3	-3.6 ‡	-1.9 *	-14.1 †
Rest of Exposed versus Internal Referents		-1.1 ‡	-1.5 *	-0.2	7.0	-1.8 †	-1.4 *	-8.1 *
Overall Trend		-4.5 §	-8.4 ‡	-4.5 *	35.2 *	-11.8 ‡	-8.9 ‡	-46.0 †
Exposure-Response Categories:								
0 < INT < 0.01	(N = 115)	-1.4 †	-1.2	-4.2 ‡	5.3	-2.4 *	-1.0	-8.6
0.01 < INT < 0.04	(N = 108)	-1.9 ‡	-2.2 *	-4.6 §	12.9 *	-3.4 ‡	-1.7	-13.1
0.04 < INT < 0.1	(N = 117)	-2.7 §	-2.0	-4.0 ‡	10.4	-4.0 ‡	-2.3 *	-17.3 *
0.1 < INT < 0.2	(N = 86)	-2.3 §	-3.2 †	-4.2 ‡	11.5 *	-4.3 ‡	-2.6 *	-17.5 †
INT ≥ 0.2	(N = 86)	-3.0 §	-3.7 ‡	-4.6 ‡	19.9 †	-7.2 §	-4.6 ‡	-27.0 ‡

Data from Young et al. (2005). Values represent differences from the respective mean score of Unexposed Referents.

Statistical notations for significance of dichotomous differences, overall trend, and exposure subcategories compared with external referents: * $0.1 > P \geq 0.05$; † $0.05 > P \geq 0.01$; ‡ $0.01 > P \geq 0.001$; § $P < 0.001$

measurements to manganese were available from personal and area samples, but individual exposure estimates were not derived. Exposure-response modeling for manganese exposures was not reported. There was exposure also to airborne lead in this work environment, making assessment of manganese related changes in the neurobehavioral tests very difficult. Nevertheless, progressive decline in alternating pronation-supination of both forearms (dysdiadochokinesis) was observed in the steel workers and not in the controls, consistent with a possible manganese effect in the steel workers. Median air concentrations were estimated to be 0.11 mg Mn/m^3 and 0.03 mg Mn/m^3 (total aerosol) in the 1970s and 1990s, respectively.

A neuropsychological survey of 143 Australian ferroalloy workers (Summers et al., 2011) examined several neurobehavioral tests in relation to cumulative manganese exposures that averaged 3.51 mg Mn/m^3-years (inhalable aerosol) and 1.20 mg Mn/m^3-years (respirable aerosol). Average exposures were 0.38 mg Mn/m^3 (inhalable, range 0.01–3.90) and 0.12 mg Mn/m^3 (respirable, range 0–0.90).

The study lacked a control group, but analyses of exposed workers showed significant associations between cumulative respirable exposures and several outcome measures (digit symbol coding; a trail making test; and the Stroop color word trial). Using hierarchical linear regression, the authors included measures of estimated full scale IQ, educational level, and age, as well as cumulative manganese exposure. Small, but statistically significant, mean effects of manganese were observed and these were of similar magnitude (but opposite in sign) to the contributions of education level.

Welders and nearby workers are other groups who are exposed to manganese, in the form of very fine, respirable particles in welding fume. Antonini (2003) has provided a detailed review of welding operations and the toxic hazards associated with this activity.

Bowler and colleagues (2006) examined manganese exposures, neurobehavioral tests and lung function in 43 bridge welders who were welding in confined spaces and using little respiratory protection. The mean exposures ranged from 0.01–0.38 mg Mn/m^3 (total dust), with more than half averaging greater than 0.2 mg Mn/m^3, while the group mean was 0.21 ± 0.08 (SD) mg Mn/m^3 (total dust). Significant exposure-response relationships were noted for a manganese CEI and for blood manganese levels in relation to neuropsychological tests reflecting a range of functions. This study confirms that welders are indeed at risk of manganese-related adverse neuropsychological effects but exposure levels were generally high among this group and do not help establish an exposure limit that might be protective of welders. It was clear, however, that an exposure limit of 0.2 mg Mn/m^3 total dust was too high to protect welders from the adverse effects of manganese.

Ellingsen and colleagues (2008) performed neurobehavioral tests on 96 Russian welders and 96 age-matched referents. The geometric mean exposures for the welders was 0.12 mg Mn/m^3 (respirable aerosol, range: 0.007–2.23), and they had worked an average of 13.5 years. Workers were divided into three equal groups based on exposure levels. Significantly decreased performance on the finger tapping and digit symbol tests was observed in the highest exposure group (geometric mean exposure 0.42 mg Mn/m^3). A dose-response relationship was observed between finger tapping decrements (relative to referents) and manganese exposure groups. Hand tremor and postural steadiness were not associated with exposure levels.

In a novel study of apprentice welders, Laohaudomchok and colleagues (2011) examined several tests of neurobehavior and mood states before and after a work shift, and related these to respirable levels of manganese particles measured over the same work period. They found an increase in reaction time and some deterioration in a novel handwriting test in relation to increasing cross-shift exposures to manganese. Although the numbers were small, workers exposed to levels > 0.02 mg Mn/m^3 showed a higher rate of decreasing tests than those exposed to levels ≤ 0.02 mg Mn/m^3 (5 of 6 versus 9 of 17, respectively).

In a detailed study of seven welders and seven controls, Sen and colleagues (2011) performed MRI scans and several neurobehavioral tests to assess where manganese deposited in the brain and how this correlated with neurobehavioral testing. Relative to controls, welders had evidence of manganese accumulation in the olfactory bulbs (OB), frontal white matter (FWM), globus pallidus (GP) and putamen. Motor performance (Grooved Pegboard test) was worse for dominant and nondominant hands in welders relative to controls. Dominant hand changes were associated with MRI intensity in FWM, GP, putamen and frontal grey matter, whereas nondominant hand scores correlated best with FWM. Average cumulative exposure was 0.88 ± 0.57 (SD) mg Mn/m^3-years and average duration of exposure was 24.1 ± 15.5 years, yielding an average exposure level of 0.037 mg Mn/m^3 (respirable aerosol). The number of subjects is small, but the data indicate detectable manganese in the brain at chronic exposure levels that correlate with subtle changes in neurobehavioral function. The mean exposure intensity is consistent with other studies cited above that show effects in the range of 0.03 to 0.04 mg Mn/m^3 (respirable aerosol).

Iregren (1999) reviewed 13 studies of manganese-exposed groups of workers that used psychological test methods, and concluded that, taken one at a time, all of the studies had methodological flaws; however, when evaluated in their entirety, all of the studies (with one exception) indicated some effects attributable to manganese exposure, and the effects were observed always in the neurobehavioral functions where they were expected. Based on the weight of evidence, manganese adversely affected workers' performance at exposure levels presently found in industry, and that studies indicated effects on the CNS below 0.20 mg Mn/m^3 (total aerosol).

Exposure-Response Modeling for Human Studies of Neurological/Neuropsychological Endpoints

Several exposure-response models have been described, with derivation of health-based exposure limits (Table 2). Based on the initial Roels et al. study (1987a, b), the U.S. EPA (1993) calculated a LOAEL (Health Equivalent Concentration, HEC) for respiratory effects of 0.34 mg Mn/m^3 total aerosol. A no-observed-adverse-effect level (NOAEL) (HEC) of 0.05 mg Mn/m^3 total aerosol was calculated based on the second Roels et al. study (1992). In view of the near equivalence of the geometric mean total dust concentrations in the Roels et al. first and second studies (0.94 and 0.95 mg Mn/m^3, respectively), there may, in fact, be little difference between the LOAEL (HEC) and the NOAEL (HEC) in terms of air concentrations; however, differences in the forms of manganese (MnO_2 versus mixed oxides and salts) to which workers in the two studies were exposed made it difficult to compare these values quantitatively (U.S. EPA, 1993).

The ATSDR statement on manganese and its associated health effects (ATSDR, 2000) provides a Minimum Risk Level (MRL) of 4×10^{-5} mg Mn/m^3, respirable aerosol, which was derived for chronic inhalation exposure to manganese. The sensitive endpoint used as the basis for this MRL was neurological effects among manganese-exposed workers. The ATSDR authors derived the MRL using a surrogate NOAEL value of 0.074 mg Mn/m^3 (respirable aerosol) that was obtained using BMD analyses of raw data from the second study by Roels et al. (1992). A similar NOAEL of 0.07 mg Mn/m^3 (respirable aerosol) was derived from the work of Iregren (1990) using BMD analysis of the individual workers' exposure and response data. The ATSDR thought these estimates were consistent with the NOAEL of 0.051 mg Mn/m^3 (median respirable particle exposure) reported for U.S. workers in a metal producing plant (Gibbs et al., 1999).

Clewell and colleagues (2003) performed an occupational risk assessment using data from the study of Roels et al. (1992). The authors used BMD as the basis for recommending an exposure guideline. In terms of current respirable exposure concentrations, the lowest benchmark dose derived from Roels' data was 0.150 mg Mn/m^3, associated with decreased hand-eye coordination. The BMDs for visual reaction time and hand steadiness were 0.5 and 0.4 mg Mn/m^3, respectively. Based on this analysis, an occupational 8-hour TWA exposure level of 0.2 mg Mn/m^3 (respirable aerosol) was recommended. The data of Gibbs et al. (1999) yielded a lower BMD of 0.09 mg Mn/m^3 (respirable aerosol).

However, there was a problem with the Clewell et al. (2003) analyses that likely led to underestimation of an exposure guideline. Clewell et al. did not have access to data in which the reported LOAEL values were lower than found by Roels et al. (1992) or Gibbs et al. (1999). In particular, the findings of Mergler and coworkers (1994) and Lucchini and colleagues (1999) were not available for the BMD analysis, and these studies had lower NOAEL levels than those considered by Clewell's group; subsequent studies have also shown lower NOAEL levels

(Bast-Pettersen et al., 2004; Young et al., 2005; Park et al., 2006).

Park and colleagues (2006) undertook a BMD analysis of the data collected by Bowler and coworkers (2006) on confined space welders in California. Four neurobehavioral outcomes were modeled against cumulative and average Mn exposure levels (total aerosol) among these workers, and each outcome showed an exposure-response relationship using linear regression models. The authors concluded that: "The prevalence of attributable neurological impairment after the equivalent of 2 years at levels of 0.2 mg/m^3 was 15–32%, depending on the definition of impairment. A prevalence of 2–5% excess impairment would be expected after 2 years at 0.02–0.05 mg/m^3 Mn." The latter estimate is again in the range of LOAELs reported by other studies.

Two meta-analyses have been attempted using data from some of the above epidemiologic studies of manganese workers (Greiffenstein and Lees-Haley, 2007; Meyer-Baron et al., 2009). Greiffenstein and Lees-Haley (2007) concluded that confounding variables (age, SES, education, etc.) explained much of the apparent manganese-related adverse effects observed among the various studies they examined. (Summers and coworkers, 2011, made a similar observation that education and general IQ contributed more to explaining the tests of neurobehavior that they used than did manganese. However, in several cases Summers' data showed that contributions from manganese were similar in statistical significance to education, and in one case exceeded the contribution of education and IQ combined. Thus, the possible effects of manganese in Summers' population should not be dismissed as unimportant.)

Meyer-Baron and coworkers (2009), using many of the same studies as Greiffenstein and Lees-Haley (2007), found significant manganese-related effects on neurobehavioral functions after adjusting for likely confounders. In part, the discrepant findings for these two meta-analyses must relate to subtle differences in the analytical methods, but both analyses suffered from using single data points for each study in relation to exposure and effect. Allowing for the variance (SD) about the study means fails to capture exposure-response relationships within each study, and it is those exposure-response relationships that most inform the derivation of this TLV.

Reproductive Studies in Humans

Manganese has been reported to cause male reproductive problems, including infertility (Lauwerys et al., 1985), loss of libido, and impotence (Rodier, 1955). Also, the hypothalamus is a site of Mn accumulation, and disturbance of the hypothalamic-pituitary-gonadal axis hormones might be expected based on animal studies (Deskin et al., 1980, 1981).

Lauwerys and colleagues (1985) examined fertility in 85 male workers producing manganese salts (carbonate, dioxide, sulfate) from concentrated ore. The airborne levels of manganese on personal samples were 0.07–8.61 mg Mn/m^3 total dust (arithmetic, median and geometric mean values were 1.33, 0.97 and 0.94 mg Mn/m^3 total dust, respectively). The authors used the questionnaire method of Levine and co-workers (1980) to assess male workers for impaired fertility. Questions covering duration of employment, residence, smoking, and drinking habits were included. A control group of 81 male workers never occupationally exposed to manganese was used for comparisons. No marked difference was found between exposed and control groups with regard to workers' ages, the ages of their wives, the ages of wives at marriage, age differences between husband and wife, duration of employment in the plant, smoking habits, alcohol consumption, educational level, and professional activity of spouse.

The numbers of children born to manganese workers in the age groups 16–25 years and 26–35 years during periods of exposure to manganese were significantly lower than expected. There was no indication that factors other than manganese might account for the marked difference between the control and manganese-exposed groups. This study suggests that a TWA exposure to manganese dust of 1 mg Mn/m^3 (total aerosol) may be sufficient to interfere with male reproductive function and cause a significant deficit in the number of children born to manganese-exposed men.

TABLE 2. Summary of Human Studies with NOAEL and LOAEL Levels Considered in Establishing a Manganese TLV–TWA (*studies in bold italics represent reanalysis of prior data*)

Health Effects	Exposure Duration (yr)	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Study Referenced Manganese Species
Respiratory (pneumonia)	NS		3.6 (T)	Lloyd Davies (1946) MnO_2
Respiratory (cough, decreased lung function)	1–19 years		0.97 (T)	Roels et al. (1987a, b)
Neurological (decreased reaction time, short-term memory, hand steadiness)			0.97 (T)	Mn salts and oxides
Hematological			0.97 (T)	Lauwerys et al. (1985)
Male reproduction (decreased fertility)			0.97 (T)	
Respiratory	5.3 years		0.18 (R)	Roels et al. (1992)
Neurological (impaired visual time, eye-hand coordination, hand steadiness)	(mean)		0.036 (R)	MnO_2
		†0.15 (R)		***Clewell et al. (2003)***
		****0.07 (R)***	***[1]0.05 (R)***	***ATSDR (2000)***
			[2]0.02 (R)	***Present analysis***
			[3]0.007 (R)	***Present analysis***
Endocrine			0.18 (R)	***Present analysis***
Neurological (decreased reaction time, finger tapping)	1–35 years (2.6 median)		0.14 (T) (median)	Iregren (1990) MnO_2
		****0.07 (R)***		***ATSDR (2000)***
Neurological (postural sway with eyes closed)	1.1–15.7 years		1.59 (T)	Chia et al. (1993) MnO_2
Neurological (decreased motor function)	16.7 years (mean)		0.032 (R)	Mergler et al. (1994) NS (Mn alloy workers)
Neurological (decreased finger tapping, symbol digit, digit span, additions)	1–28 years		NS	Lucchini et al. (1995) Mn oxides
Neurological	12.7 years (mean)	0.051 (R) (median)		Gibbs et al. (1999) NS
		†0.09 (R)		***Clewell et al. (2003)***
Neurological (decreased behavioral tests)	11.5 years (mean)		0.097 (T) 0.038 (R) (geo mean)	Lucchini et al. (1999) MnO_2, Mn_3O_4
Neurological (decreased behavioral tests)	18.2 years (mean)		0.01–0.04 (R)	Young et al. (2005) NS (Mn smelter workers)
Neurological (decreased behavioral tests)	1.25 years (mean)		0.02–0.05 (T)	Park et al. (2006) NS (Welders)
Neurological (tremor)	2.1–41 years (20.2 mean)		0.30 (I) 0.036 (R)	Bast-Pettersen et al. (2004) NS (Mn alloy workers)

Abbreviations:
NS: Not Stated
T: "Total Dust"
R: Respirable Particulate Matter
I: Inhalable Particulate Matter

* Based on BMD method applied by ATSDR (2000)
† Based on BMD method applied by Clewell et al. (2003)
[1,2,3] Present analysis (*see* text) — abnormal hand steadiness in 5%, 2.5%, and 1% of manganese workers, respectively

TLV® Chronology

Manganese
1948–1959: TLV–TWA, 6 mg/m^3
1960–1962: TLV–TWA, 5 mg/m^3
1963–1969: TLV–CEILING, 5 mg/m^3

Manganese and Compounds
1970–1981: TLV–CEILING, 5 mg/m^3, as Mn

Manganese Fume
1977: *proposed*: TLV–TWA, 1 mg/m^3, as Mn
1979–1994: TLV–TWA, 1 mg/m^3, as Mn; STEL, 3 mg/m^3, as Mn

Manganese Dust and Compounds
1982–1987: TLV–CEILING, 5 mg/m^3, as Mn
1986: *proposed*: TLV–TWA, 5 mg/m^3, as Mn
1988–1994: TLV–TWA, 5 mg/m^3, as Mn

Manganese, Elemental and Inorganic Compounds
1992: *proposed*: TLV–TWA, 0.2 mg/m^3, as Mn
1995–2012: TLV–TWA, 0.2 mg/m^3, as Mn
2003: *proposed*: 0.03 mg/m^3, as Mn, Respirable particulate matter; withdrawn 2004
2009: *proposed*: TLV–TWA, 0.02 mg/m^3, as Mn, Respirable particulate matter, and 0.2 mg/m^3, as Mn, Inhalable particulate matter; A4, Not Classifiable as a Human Carcinogen; withdrawn 2011
2011: *proposed*: TLV–TWA, 0.02 mg/m^3, as Mn, Respirable particulate matter, and 0.1 mg/m^3, as Mn, Inhalable particulate matter; A4, Not Classifiable as a Human Carcinogen
2013: Adopted: TLV–TWA, 0.02 mg/m^3, as Mn, Respirable particulate matter, and 0.1 mg/m^3, as Mn, Inhalable particulate matter; A4, Not Classifiable as a Human Carcinogen

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