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**Welding and Exposures to Manganese
Assessment of Neurological Adverse Effects**

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Abstract

Manganese (Mn) is a required trace element for growth and reproduction with Mn deficient diets resulting in growth retardation, skeletal and joint cartilage abnormalities, fetotoxicity, testicular degeneration, diabetes and vestibular dysfunction. Mn requirements range from 30-100 ppm in the diet for various species. Man ingests 2.3-7 mg Mn/day. Calculated absorbed doses of Mn for man range from 80-450 $\mu\text{g/day}$ from dietary sources.

Excessive body burden of Mn can occur from excessive exposures from intravenous supplementation or from occupational exposures or from decreased Mn excretion seen with chronic liver disease. Exposures during welding have ranged from 0.024-0.22 mg/m^3 in the last decade with higher exposures when there was GMAW welding, no ventilation or welding on manganese alloy steel. Exposures associated with manganism have been above 3 mg Mn/m^3 and have occurred primarily in the mining and manganese alloy fabrication industries. Manganism is an illness that includes extrapyramidal symptoms and findings (parkinsonism), psychiatric symptoms, intentional tremor, dystonia, and incoordination. In non-human primates, no clinical or pathological changes occur when exposures are limited to 3 mg Mn/m^3 or less. Clinical findings of manganism respond readily to treatment with chelating agents (EDTA or PAS), even when treatment is first started years after exposure ceases.

Manganism differs both clinically and pathophysiologically from Parkinson's Disease (PD). The latter involves damage to dopaminergic neurons in the substantia nigra while with manganism there is damage downstream from this dopaminergic pathway. In PD, where there are decreased levels of dopamine, treatment with L-dopa can result in clinical improvement while in manganism, where dopamine levels are generally normal, L-dopa is usually ineffective. Studies by Racette and his colleagues have been used to hypothesize that welders may develop classical PD at an earlier age than the general population. The age distribution in these populations was, however, similar to other PD populations seen

in physician offices. Further, studies of PD patients have not identified an increased prevalence of either welders or exposure to Mn in these populations.

Exposures to Mn at levels below those associated with a risk of manganism can result in changes found on sensitive neurophysiological studies including tests of eye-hand coordination, hand steadiness (tremor), and simple reaction time. When exposure to Mn is discontinued, neurophysiological abnormalities improve or disappear. These neurophysiological studies are used for worker monitoring as a supplement to industrial hygiene monitoring studies. Further these studies have been used to define acceptable exposure levels to Mn. Various agencies have set acceptable continuous (environmental) exposures to Mn at levels ranging from 0.05-31.5 $\mu\text{g}/\text{m}^3$. In adults, such exposures, assuming 100% absorption of inhaled Mn, would result in daily absorbed doses of Mn ranging from 0.05-470 $\mu\text{g}/\text{d}$, similar (at least at the upper range) to those seen from dietary sources. The current workplace threshold limit value for Mn is 200 $\mu\text{g}/\text{m}^3$.

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Welding and Exposures to Manganese. Assessment of Neurological Adverse Effects

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I. Introduction

Manganese (Mn) is a required trace element for growth and reproduction. Manganese deficient diets are associated with growth retardation, skeletal and joint cartilage abnormalities, fetotoxicity and vestibular dysfunction with associated ataxia in rodents, pigs, chicken and cattle. Deficient diets are also associated with testicular degeneration, increased infant mortality, pancreatic hypoplasia, and inability to utilize glucose (diabetes). Ataxia and joint problems are thought to be secondary to interference with normal cartilage development, including lack of development of otoliths necessary for normal vestibular function. Manganese requirements in these species range from 30-100 ppm in the diet. Unequivocal evidence of manganese deficiency has, however, not been demonstrated in man (Underwood, 1971).

The major source of non-occupational exposure to manganese is from the diet with mean intakes in man ranging from 2.3-7 mg/day. Manganese salts are poorly absorbed with 3-4% of the ingested dose absorbed in rodents (Underwood, 1971). If this absorption rate prevails in man, the average absorbed dose Mn would range from 80-200 µg/day. WHO (1981) calculated that the absorbed dose from ingested Mn ranges from 100-450 µg/day based on a 5% gastrointestinal absorption. The AMA recommendation for intravenous Mn supplementation in TPN is 150-800 µg/day (Nagatomo, et al., 1999).

II. Mn Exposure with welding

Mn is contained either in base metal (mild steel or ferromanganese alloy) that is being welded or in the welding consumables. Mn concentrates in welding fume (compared to the weld) with amounts found in the following ranges (Minni et al., 1984; IARC, 1990):

MMA/SS: 1.4-14%
GMAW/SS: 4.8-12.6%
MMA/MS: 2.5-5.9%
GMAW/MS: 3.9-7.3%:

where:

MMA: manual metal arc welding

GMAW: inert gas metal arc welding (also known as MIG welding)

SS: stainless steel

MS: mild steel

Exposures to total welding fume correlate with exposures to Mn: as the percentage of Mn increases, exposure potential would increase as well. Welding fume is respirable.

Ventilation improvements will decrease exposure. In most countries, ventilation rates are now designed to maintain fume levels at 2-4 mg/m³. Exposure levels have been decreasing by a factor of 2 per decade since the 1940s (IARC, 1990).

Actual exposure levels to Mn during welding will vary with major factors affecting exposure levels being the type of welding, type of base metal being welded and the amount of ventilation. As can be seen from the table below, for welding on stainless steel, exposures in the last decade have ranged from 0.024-0.061 mg/m³ with higher exposures when there is GMAW welding or no ventilation. For welding on mild steel, studies done during the last decade have shown exposures of 0.25-0.60 mg/m³ with increases in exposures with poor ventilation. As with SS welding, GMAW welding usually results in higher exposures though exposures as low as 0.032 mg/m³ have been measured with GMAW welding of MS in an unventilated area. Although welding fume is respirable, measurements of respirable Mn levels have been less than those of total Mn levels (Smargiassi et al., 2000).

Mn exposures can also be assessed by exposures peculiar to a specific job type. Rappaport et al. (1999) evaluated worker-obtained measurements of breathing zone total Mn. Sampling lasted for 62-525 min/day. Workers exposed to Mn were welders (19), boiler makers (5), iron workers (7) and pipe fitters (14). Measured mean levels of Mn exposure ranged from 0.474-0.652 mg/m³ for boiler makers, 0.134-0.222 mg/m³ for iron workers, 0.070-0.097 mg/m³ for pipe fitters and 0.062-0.067 mg/m³ for welders. Susi et al. (2000) used task-based exposure assessment model (T-BEAM) to evaluate exposures to construction workers. Welding activities included tank bottom replacement of a boiler using air carbon arc cutting and shielded metal arc welding of carbon steel; welding and cutting carbon steel pipe and pipe supports (4 locations); welding and torch cutting of steel stringers and walkways; plasma arc welding and cutting of stainless steel; SMA and GMAW welding of stainless steel and mild steel, and SMA welding of carbon steel pipe. Total Mn levels averaged 0.20-0.28 mg/m³ (range 0.0005- 1.31) without local exhaust ventilation and 0.07 mg/m³ (range 0.001-0.47) with local exhaust ventilation. Logged samples in 7% of pipe fitters, 15% of iron workers and 72% of boilermakers exceeded 0.2 mg/m³. Boilermakers were only evaluated in 1995. Local exhaust ventilation had the most striking effects on thermal cutting (94% decrease in total fume) and welding/thermal cutting (a 79% decrease). Indoor exposures were approximately ½ those of outdoor exposures. Both studies had the weakness that sampling was done by workers, not trained industrial hygiene personnel.

Table 1: Manganese exposures during welding

Type of welding	Ventilation	Respirable Mn exposure (mg/m ³)	Total Mn exposure (mg/m ³)	References
GMAW/MS	None		0.032-0.073	Franek,1994
MMA/FMA	Out of doors		4.0-7.2	Franek,1994
MMA/SS	Local exhaust		0.024 (mean)	Karlsen et al., 1994
MMA/SS	None		0.120 (mean)	Karlsen et al., 1992
MMA/MS	?		0.36 (mean)	Jarvisalo et al., 1992
GMAW/SMA of MS	Local exhaust	0.094	0.144-0.20 (gm)	Smargiassi et al., 2000
SMA/MS	?		0.14	Akbarkhanzadeh, 1979
SMA/GMAW cutting on MS	None-local exhaust		1.4-3.1 (mean)	Ulfvarson, 1981
GMAW/MS (90%) GMAW/SS (<10%)	Dilutional		0.5 (mean)	Korczynski, 2000
MMA/SS	Local exhaust		0.13 (mean)	Matczak and Chmielnicka, 1993
SS	Local exhaust/dilutional		0.029 (mean)	Kucera et al., 2001
MMA/MS	Dilutional		1.2 (mean)	Evans et al., 1979
MMA/MS or SS	Dilutional		0.25 (median)	Vasconcelos et al., 1996a,b
GMAW/MS	Dilutional		0.08 (median)	Vasconcelos et al., 1996a,b
GMAW/MS	+/- local exhaust		0.78-3.43 (mean)	Bellido-Milla et al., 1995
MMA/MS	+/- local exhaust		0.60 (mean)	Bellido-Milla et al., 1995
MMA/SS	?		0.061 (median)	Wang et al., 1994
GMAW/MS	?		0.389 (median)	Wang et al., 1994
MMA/MS	?		0.43 (mean)	Teresa et al., 1997

where: SMA: shielded metal arc welding; IA: inconel alloy; FMA: ferromanganese alloy
g.m.: geometric mean

III. Manganese metabolism

Uptake and excretion of manganese

In rats, peak blood values are reached with oral dosing of MnCl_2 in 2 hours. With intratracheal dosing with MnO_2 , peak blood levels are reached in 8 days while with MnCl_2 the peak blood levels occurred in 1 hour. With acute inhalation of MnCl_2 in tracer amounts in monkeys, peak brain levels occur after 40-50 days (Andersen et al., 1999).

Manganese (Mn) is apparently oxidized by ceruloplasmin and the trivalent Mn binds to the iron carrying protein, transferrin. Brain uptake of Mn occurs via transferrin receptors located in various brain regions. Transferrin receptors are in the capillaries in the CNS and transferrin enters brain endothelial cells via receptor-mediated pinocytosis. Mn-accumulating regions in the brain (nucleus accumbens and caudate-putamen) are high in transferrin receptors. From these areas, Mn appears to move by neuronal transport to accumulation sites in the pallidum, thalamic nuclei and substantia nigra. (Andersen et al., 1999).

Manganese is excreted via the bile and gut. Consequently, individuals with cholestatic liver disease are at a risk of developing Mn-associated CNS disease (Andersen et al., 1999). 20-50% of patients who have chronic liver failure develop severe parkinsonism with generally a poor response to L-dopa. Such patients have alterations on MRI that are seen with manganism and plasma Mn levels are elevated (Olanow, 2004). Hine and Pasi (1975) describe such a worker who developed manganism while working as a clay mixer at a ceramics plant where he added 50# bags of MnO_2 to a hopper. This operation was repeated 4-6 times per shift for 13 years. Workplace air Mn levels were $<5 \text{ mg/m}^3$. He had alcoholic cirrhosis and ascites. He developed an acute brain syndrome with confusion, bizarre behavior, hallucinations and ataxia, continuous tremors and weakness of his legs, a positive Babinski sign, rotatory nystagmus. On a follow-up clinical examination 9 months later, there were no neurological abnormalities or symptoms. An EDTA challenge resulted in increased urinary Mn excretion.

Retention

Following inhalation, a considerable amount of Mn is retained in the lungs providing a depot that slowly releases Mn to the bloodstream resulting in prolonged CNS exposure (Newland et al., 1989). The clearance of particles from welder's lungs is estimated to be 20% per year with material in the lungs representing exposure over the preceding 5-10 years (Sjogren, 1994). Newland et al. (1987) exposed macaca monkeys to $^{54}\text{MnCl}_2$ aerosols. Half-lives for Mn leaving the chest ranged to 187 days. Head levels peaked in 40 days after dosing and remained high for 1 year after dosing. With systemic dosing, Mn cleared more rapidly from the head than after inhalation. Long half-lives in the head (on the order of 600 days) reflect both slow disappearance and replenishment.

Stauber et al. (1987) noted that the biological half-life of Mn in humans is 4 days for the fast fraction (30% of the absorbed dose) and 40 days for the slow fraction. Mena et al. (1967) hospitalized 14 healthy manganese miners for 20-30 days for Mn turnover studies. They compared these miners with 13 miners with manganism whose last exposure was

any where from immediate to 25 years (median 5 years) at the time of the evaluation. Among the total population of 114 “healthy” miners, 23 showed cogwheel rigidity without tremor. These 23 were not among the 14 chosen for turnover studies. Half-lives for total body turnover of ^{54}Mn were 35.5 days for controls, 12.5 days for healthy miners and 26.5 days for miners with manganism. The most neurotoxic ores appear to be ones where Mn has a valence state higher than 2. Comparing their results to previous work in experimental animals and man, the authors felt that it was likely that the increased turnover rate in healthy miners represents an increased tissue level of this metal.

Cotzias et al. (1968) investigated the biological half-life of manganese using a ^{54}Mn tracer in workers with and without a history of Mn exposure. The half-life of Mn in whole blood ranged from 1.28-2.19 min and from 37-62 days in the head with no significant differences depending on whether or not the individuals had a history of exposure to Mn or a history of manganism. When the authors measured actual declines when a Mn poisoned worker was removed from work, urine Mn excretion halved initial values approximately 45 days after removal. Hair levels were 53 ppm at removal vs. 21.6 ppm three months later. Blood decreased from 4.0 $\mu\text{g}\%$ to 2.0 $\mu\text{g}\%$ at 11 mos after removal.

Dastur et al. (1971) treated 12 monkeys with ^{54}Mn maleate intraperitoneally and followed them for 278 days. They found that the brain is peculiar in that it retains Mn for relatively long periods of time out of proportion to that retained by all other organs. At the end of 278 days the highest levels were in the cerebellum, lentiform nucleus, basal ganglia, caudate nucleus, brain stem and thalamus with low levels in other body tissue. The half-life for the whole body was 95 days. The authors felt that a selective high retention of Mn in the brain could be the basis for damage to the brain.

Distribution

When comparing normal miners with normal controls, Cotzias et al. (1968) found that tissue levels of ^{55}Mn in serum, spinal fluid, urine, hair, skin and muscle similar but blood levels 2 fold higher (mean of 2.56 $\mu\text{g}\%$ vs. mean of 1.17 $\mu\text{g}\%$).

Normandin et al. (2002) exposed rats to aerosols of Mn for 30 hours a week for 13 weeks. Although there were elevated Mn levels in all areas of the brain, the highest levels were found in olfactory bulb and caudate/putamen with levels increasing in a dose-dependent fashion.

In a second study, Normandin et al. (2004) exposed rats for 30 hours per week for 13 weeks to 3000 $\mu\text{g}/\text{m}^3$ Mn as Mn phosphate or Mn phosphate/sulfate or to 4000 $\mu\text{g}/\text{m}^3$ as metallic Mn. Brain Mn levels were higher with exposure to Mn salts. In the striatum, Mn levels increased by 76% with metallic Mn exposure, 116% with Mn phosphate exposure and 147% with Mn phosphate/sulfate exposure. No neurobehavioral changes were seen with metallic Mn or Mn phosphate exposures but there was a decrease in ambulatory activity with Mn phosphate/sulfate exposure.

Eriksson et al. (1992) evaluated macaca monkeys by magnetic resonance imaging (MRI) scans after dosing them subcutaneously with manganese (IV) oxide. The manganese accumulated in the globus pallidus, putamen and caudate nucleus.

Dopamine effects

Dopamine (DA) is a transmitter for brain neurons involved in regulating movement and motivated behavior (dopaminergic neurons). In Parkinson's Disease (PD) there is selective loss of DA-containing neurons. The major effect of Mn toxicity, however, is on cells of striatum and globus pallidus which are not dopaminergic (Langston et al., 1987). A fluorodopa positron emission tomography (PET) scan provides an index of prestriatal dopaminergic function. There is reduced striatal uptake in PD, particularly in the posterior putamen. In early PD, there is loss of dopaminergic cells in the substantia nigra pars compacta, the primary focus of neurodegeneration in PD. Olanow et al. (1996) treated rhesus monkeys with weekly intravenous (iv) injections of MnCl₂. Two developed parkinsonian syndrome not responsive to levodopa. Striatal dopamine levels were normal in the 2 animals with parkinsonian syndrome.

Although movement disorders may be similar between PD patients and those with manganism, the brain neurochemical effects seen with Mn exposure differ from those seen with PD. Fluorodopa positron emission tomography (PET) shows integrity of the nigrostriatal dopamine pathways, reflecting dopaminergic uptake of the tracer by nigral cells. In humans and non-human primates intoxicated with Mn, fluorodopa PET uptake is normal (Pal et al. 1999). Similar findings are seen in rodents exposed to Mn. Witholt et al. (2000) dosed rats with Mn intraperitoneally (ip) at dose levels of 4.8 mg/kg, 3 times a week for 5 weeks (a total of 72 mg/kg). Mn treatment did not result in striatal dopamine depletion. Mn exposure increased whole brain Mn levels 3.4 fold and was associated with behavioral changes, including gait abnormalities, impaired balance and decreased arousal. That fluorodopa PET studies are abnormal in PD but normal with Mn toxicity suggests that nigrostriatal pathways are relatively spared in manganism. PET studies with the D2 receptor ligand raclopride show reduced uptake in manganism, further supporting the hypothesis of postsynaptic striatal loss (Shinotoh et al., 1997; Kim et al., 1999a). In a study of 6 patients with manganism, fluorodopa PET studies were normal. Similarly, monkeys dosed with Mn to the point of intoxication had normal fluorodopa studies (Olanow, 2004). Wolters et al. (1989) evaluated 4 workers who had mild manganism after working in the same manganese smelting department for 4 or more years. [¹⁸F]6-fluorodopa PET scans did not differ from those of 21 controls while maximum striatal activity was decreased in 13 patients with PD. Huang et al. (1998) followed 5 patients who had developed manganism for 10 years. Their clinical course deteriorated without further exposure. PET scanning showed no significant fluorodopa uptake but there was widespread decline in cortical glucose. There was no evidence of impairment of dopaminergic nerve function.

PD patients respond to L-dopa: they have degeneration of dopaminergic neurons in the substantia nigra but preservation of dopamine receptors in striatal neurons. In contrast, damage to the striatum or pallidum results in damage to downstream neurons and dopamine receptors that precludes satisfactory response to L-dopa. With Mn intoxication in humans, rodents and non-human primates, there is damage to the substantia nigra pars reticularis and globus pallidus with relative sparing of the nigrostriatal system and other areas affected by PD, such that the effectiveness of L-dopa is generally less. If damage of the globus pallidus is not complete (such as in some CO poisoning cases), there may be

enough efferent output preserved for augmentation of striatal dopamine levels with Levodopa to be beneficial (Bleecker, 1988). Wolters et al. (1989) noted no sign of disturbance of [¹¹C]-L-dopa utilization in the striatum where it is decarboxylated by dopaminergic neurons. Further [¹¹C]-raclopride binding was normal, indicating that D2 receptor density had been maintained. The latter 2 findings are prerequisites for successful treatment with L-dopa. Huang et al. (1989) treated 6 workers who developed manganism while working in a ferromanganese alloy plant. All responded well to treatment with L-dopa/carbidopa for 8 weeks. Blood Mn values ranged from 10.2-40.5 µg/dL (normal 0.7-1.2), scalp Mn ranges from 27.7-445.2 ppm (normal 0.1-2.2) and public hair Mn ranged from 26.7-2735.5 ppm (normal 0.3-9.8). Bonilla and Diez-Ewald (1974) also found some effectiveness of L-dopa in a rodent model. They treated rats with an average of 700 mg MnCl₂/day in drinking water for 7 months. The rats were then treated with 100 mg/kg of L-dopa. None of the animals developed muscular rigidity, tremor or limb paralysis. Histopathological studies of the caudate nucleus showed moderate changes to some neurons. Brain dopamine levels were significantly reduced with Mn treatment. Dopamine levels increased in both controls and treated animals treated with L-dopa. The response to the Mn-treated animals was greater (400% vs. 210% in controls) such that the resultant dopamine concentrations were similar to those of treated and control animals. Other studies, however, show a more pronounced dopamine effect at exposure levels that cause brain damage. Mustafa and Chandra (1971) treated rabbits with 400 mg of MnO₂ with a mean particle size of 5 µm intratracheally. Between 18 and 24 months, treated rabbits developed hind limb paralysis. At 24 months, dopamine and norepinephrine levels were reduced 21 and 58% with accompanying neuron loss and degeneration in the cerebrum, cerebellum, caudate nucleus, putamen and substantia nigra. Serotonin levels were unchanged.

Changes in dopamine levels have also been demonstrated with Mn exposures in the non-human primate model. Neff et al. (1969) injected squirrel monkeys with 2 or 3 injections of 200 mg MnO₂ over a period of 3 or 6 months. At the end of 3 months there were signs of toxicity with rigidity and resting tremors. Caudate nucleus dopamine levels were significantly depressed. At the end of 6 months, dopamine levels had increased but were still significantly below normal and serotonin levels were significantly depressed in the caudate nucleus as well. Monkeys after 6 months showed less toxic effects than after 3 months with no effects in 2, slight tremors in 3, and tremors and rigidity in one. At autopsy at 3 and 6 months there were no histological changes in any neurons or glial elements anywhere in the brain or brainstem. Eriksson et al. (1992) evaluated macaca monkeys by positron emission tomography (PET) scans after dosing them subcutaneously with manganese (IV) oxide. They evaluated [¹¹C]-nomifensine uptake, a measure of dopamine nerve terminal distribution. Over 16 months dopamine nerve endings degenerated. Eriksson et al. (1992) treated 2 macaca monkeys with 0.4 gm of Mn subcutaneously 11 times over 4 months and then a 12th time at 12 months. The monkeys developed unsteady gait, minor clumsiness and hypoactivity after 4-5 months. Findings remained constant after that. [¹¹C]-nomifensine PET scans (a specific ligand for dopamine uptake sites located in the dopaminergic nerve terminals in the striatum) showed declined binding after 2 months and reached 60% of the initial values at 12 months. In a parallel study by these authors, autoradiography with [³H]-mazindol showed loss of binding in the caudate nucleus and putamen. Both studies suggest destruction or interference with

binding to dopaminergic nerve terminals. T1-weighted MRIs showed increased signal density in the caudate nucleus, putamen, globus pallidus and internal capsule and internal capsule changes indicating gliosis or edema.

IV. Manganism

Clinical spectrum of manganism

An excellent description of manganism occurring in underground miners where exposures to 253-448 mg Mn/m³ occurred after dry drilling manganese ore in Morocco is given by Rodier (1955). He evaluated 150 workers with manganism. The prodrome of this illness is subjective with associated movements becoming difficult and dull affect followed by mental excitement, incoherence, staggering gait, impotence and somnolence. Later affected workers have insomnia. In the intermediate stage, affected subjects stutter, have a fixed jovial expression, have difficulty eating and drinking, will fall backwards with a simple push, are unable to run, have retropulsion and loss of balance when attempting to walk backward and adiadochokinesis and exaggerated reflexes on a neurological exam. In the established phase, which usually begins a few months after patients first become symptomatic, there is muscular hypertonia in extension which intensifies with movement, a staggering, spasmodic gait, and an inability to maintain balance with the feet together. Walking backwards or climbing a ladder is impossible and a half turn becomes difficult. There is a tremor and written letters become smaller. There is no facial animation with speech, hypertonia and contraction of the facial musculature, spasmodic laughter, and varus deformities of the feet.

Schuler et al. (1957) also described manganism among miners. Drilling of Mn ore resulted in exposures to Mn ranging from 0.6-46 mg/m³. 15 miners developed manganism after an average of 8.2 yrs of exposure. Symptoms included irritability, apathy, hallucinations, flight of ideas, compulsive acts, verbosity, headaches, fatigue, nightmares, muscle pains, and disturbance of speech. On neurological examination, abnormalities included hypertonia of an extrapyramidal character, expressionless face, gait changes, monotonous voice, dysarthria, and tremor. Repeated passive movements resulted in marked exaggeration of hypertonia. In some cases there was cogwheel rigidity. There was remarkable slowing of both active and passive movements of the extremities. Walking began in slow steps with the arms drooped at the sides. There was no loss in coordination. Cortical signs occurred among miners with the highest exposures.

Mena et al. (1967) describe manganism developing among 13 manganese miners. Psychomotor disturbances, including irritability, compulsive acts, emotional instability with easy laughter or crying and headaches occurred during the first month of the illness and resolved. 4 of the 13 miners with manganism experienced hallucinations. While "locura manganica" was still in evidence, patients developed general muscle weakness, difficulty in walking with loss of associated arm swinging, impaired speech then, in some, tremors, facial masking, cogwheel rigidity, increased muscle tone, and falling when trying to walk backwards. The gait was slow and shuffling. A Romberg test for instability with the eyes closed was negative. One patient had a resting pill-rolling tremor while 8 had intermittent intentional tremors. In the least affected individuals, speech defects cleared within one year of removal from exposure.

Flinn et al. (1941) evaluated 11 workers with manganism. Among the affected workers the gait was spastic in character with marked incoordination of movement, difficulty starting to walk, very short steps when first starting walking, walking on the metatarsal-phalangeal joint (cock walking), great difficulty in stopping and tending to fall backwards or forwards when walking. The voice was stuttering, monotonous with rapid running together of words and was not much louder than a whisper. There was a coarse twitching or resting tremor of the hands and arms which was increased in some cases with volitional movement and there was a well-marked tremor of the extended tongue. The Romberg test was negative but some affected workers had difficulty with heel-to-toe walking and the finger-nose-finger maneuver owing to poor muscular control. Dysdiadochokinesia was often present. No cog-wheeling rigidity was observed. There was decreased muscular strength. The authors did not see the general muscular rigidity or a pill-rolling tremor that was decreased with volitional movement that is seen in PD.

Unlike Parkinson's disease, all patients with manganism may have some degree of dystonia defined as postural instability of complementary muscle groups. The difficulty increases after saying a few words or writing a few lines. The ability to use opposing muscle groups alternately quickly is disturbed. When walking, increasing muscle stiffness limits ability to move. As further effort to use muscles occurs, patients get dystonic posturing, often accompanied by painful cramps. The tremor seen with manganism is different than that seen in PD: it may be more of a flapping quality than a pill-rolling tremor. Similar dystonic posturing has been observed in monkeys intoxicated with manganese dioxide (Barbeau et al., 1976). Other dystonic features include facial dystonia with blepharospasm, grimacing, torticollis and oculogyric crises. Rare manifestations include cranial nerve deficits (diplopia or hearing loss), corticospinal tract dysfunction with hyperreflexia and extensor plantar responses, and cerebellar deficits with pronounced ataxia (Sadek et al., 2003).

Other abnormalities seen on neurological examination include slurred speech, diminished short term memory, somnolence, unstable tandem gait, postural instability when pulled backwards, severe bradykinesia, difficulty turning rapidly, and a resting tremor made worse by intentional activities (Cook et al. 1974).

Rosenstock et al. (1971) described a worker at a ferromanganese foundry who had been exposed while operating a crane over furnaces where steel was mixed with manganese. He started work at age 22 and 14 months later became symptomatic. Symptoms and findings included irritability, impaired gait and balance, dysarthria. He continued to work for another 2 years during which time the symptoms progressed. 12 years later he was confined to a wheel chair. On examination he had bradykinesia, facial masking, a dystonic stance, retropulsion when attempting to walk, cogwheeling rigidity, resting and intentional tremors, dysdiadochokinesia, snout, glabellar reflexes and a positive Babinski reflex. His serum Mn was normal but his hair Mn was increased ranging from 29-107 ppm.

Olano (2004) evaluated 6 of 13 patients who had developed manganism with exposures to Mn in excess of 27 mg/m³. They had gait dysfunction, particularly when walking backwards, bradykinesia, micrographia, and hypophonia. 5/6 had dystonia. Postural

tremor but no resting tremor was present in 3. L-dopa treatment resulted in non-sustained improvements.

Hua and Huang (1991) evaluated 17 ferromanganese alloy factory workers (group 1) who had been exposed to $> 2\text{mg/m}^3$ Mn for an average of 11.88 years. Neurological examinations of these workers were normal. Group 2 were 4 workers who had chronic manganese poisoning, group 3 were 8 individuals with idiopathic PD and the last group was made up of 19 controls. Both parkinsonian groups had bradykinesia and rigidity without balance impairment. Brainstem evoked potential studies and CT scans were normal in both of these groups. The mean blood Mn level in group 1 was $6.72 \pm 4.2 \mu\text{g/dL}$ and, in group 2 (taken an average of 2.54 years post exposure), $2.08 \pm 1.1 \mu\text{g/dL}$. Scalp hair Mn averaged 342 ± 374 ppm in well workers and 103 ± 83 ppm in those with manganism. Urine Mn averaged $132 \mu\text{g/L}$ in the well group. Each worker received a full neuropsychological evaluation including finger tapping and the Purdue pegboard test. None of the tests of well workers in group 1 were significantly different from the control group while results of those with manganism were between PD and normals for manual dexterity (pegboard) and finger tapping. Workers with manganism also had impairments in intellectual functioning, visual discrimination of unfamiliar faces, manual dexterity, and information processing speed while motor speed, learning, and visual attention while memory was normal.

Wolters et al. (1989) evaluated 4 workers who had mild manganism after working in the same manganese smelting department for 4 or more years. Symptoms in 3 of the 4 were not sufficient to seek medical care. Findings included bradykinesia, rigidity, facial masking, diminished blinking, hypophonia, impaired dexterity, micrographia, gait abnormalities and, in 2, resting tremor. No cognitive deficits were found on neuropsychological testing.

Pathology

Pathological studies of Mn intoxicated patients show degeneration of the globus pallidus followed by less severe degeneration of the putamen, caudate nucleus and substantia nigra. There is inconsistent damage to the substantia nigra pars compacta, pons, cerebral cortex, thalamus and hypothalamus. These findings are different from those of PD where there is prominent cell damage in the substantia nigra pars compacta, locus ceruleus and dorsal nucleus of the vagus with Lewy bodies in all cases (Pal et al. 1999). Yamada et al. (1986) evaluated a worker who developed manganism 12 years after beginning working at a Mn ore crushing plant. Urine Mn was $104 \mu\text{g/L}$ and blood Mn was $3.4 \mu\text{g/dL}$. EDTA treatment increased urine Mn to $564 \mu\text{g/L}$. There was no clinical improvement with this treatment nor to L-DOPA. He died of cancer 15 years after last being exposed. At autopsy there was atrophy and loss of cells of the pallidum, putamen and caudate nucleus with the remaining cells shrunken. There was marked decrease in myelinated fibers, increase in astrocytes and proliferating glial fibers in the pallidum. The nerve cells in the thalamus and cerebral cortex were shrunken. Brain Mn levels were similar to those of controls.

Bernheimer et al. (1973) evaluated a case of manganism who developed parkinsonian symptoms at age 44. Clinical findings included rigidity, tremor, and akinesia but no mask-like facies or asymmetrical findings. The patient died after 23 years of his illness.

Findings of substantia nigra damage and dopamine decrease in the striatum were similar to cases of PD. There was bilateral atrophy and gliosis of the putamen and pallidum. Lewy bodies were present in the substantia nigra and there was neuroaxonal dystrophy in the zona reticularis.

Comparison with Parkinsonism

Parkinsonian syndrome is characterized by bradykinesia (slowness of movement), rigidity (increased muscular resistance to passive movement) with superimposed cogwheeling (waxing and waning of resistance), a resting tremor and postural reflex impairment (impaired balance). These cardinal signs are accompanied by a host of secondary findings including facial masking (paucity of facial expression), diminished spontaneous blinking, stooped posture, shuffling or propulsive gait, soft and hesitant speech, hesitancy on initiation of movement and micrographia (small handwriting). Dopamine cells are found in the substantia nigra of the midbrain to the basal ganglia or striatum of the cerebral hemispheres, composed of the caudate, putamen and globus pallidus. Any insult that interferes with dopamine-mediated neurotransmission in this system can cause all of the signs of parkinsonism. Parkinson's disease (PD) is a specific disorder with pathological lesions principally in the substantia nigra (Tanner, 1992). PD, which presents with a gradual onset, has predominantly asymmetrical features (rigidity, bradykinesia, and resting tremor) in most patients (Racette et al., 2005a).

Brain scan findings

Kim et al. (2002) measured the integrity of the nigrostriatal dopaminergic pathway with a [^{123}I]- β -CIT SPECT scan where there is binding to dopamine transporter protein. In idiopathic Parkinson's disease there is severe reduction of striatal binding of β -CIT. With manganism, where damage is downstream from the nigrostriatal dopaminergic pathway, one would expect no increase in uptake.

Shinotoh et al. (1997) evaluated 4 patients with manganism from exposure in a ferromanganese factory. Positron Emission Tomography (PET) scans showed normal fluorodopa uptake in the putamen and caudate and raclopride binding was mildly reduced in the caudate and normal in the putamen consistent with integrity of the nigrostriatal pathway.

Because Mn is paramagnetic, relevant MRI signals may be seen in basal ganglia if concentrations of Mn are high (Calne et al., 1994). In a study of 6 patients with manganism, Olano (2004) found hyperintensities in the globus pallidus and striatum on T-1 weighted MRI images consistent with Mn deposition in these areas. Fluorodopa PET studies were normal.

Cerebral glucose metabolism was studied in the 4 patients with manganism and 17 age-matched controls using [^{18}F]2-fluoro-2-dexoxyglucose PET scans. Glucose consumption was decreased in all brain areas compared to controls with the lowest levels found in the caudate and putamen. Similar wide spread decreases in glucose consumption is seen in PD (Wolters et al., 1989).

Nagatomo et al. (1999) report on 2 cases of manganism where an Mn supplement had been added to the total parenteral nutrition (TPN) solution. In the first case marked confusion, rigidity, facial masking and vertical gaze palsy developed in a 68 year old woman 3 months after starting TPN. Her serum Mn was 4.2 µg/dL. An MRI showed hyperintense T1-weighted signals of the basal ganglia, particularly the globus pallidus. She was treated with EDTA for 5 days with urine Mn increasing from 10-20 µg/L to 150-180 µg/L. The abnormal MRI resolved in 3 months. In the 2nd case, a 70 year old man developed signs of manganism after 4 months of TPN with an Mn-supplemented solution. He developed a gait disturbance, confusion, marked rigidity, facial masking and a resting tremor. An MRI showed hyperintense T1-weighted signals of the basal ganglia, particularly the globus pallidus. His serum Mn was 5.1 µg/dL. Treatment with EDTA resulted in an increase of his urine Mn from <10 µg/L to 210 µg/L. There was gradual improvement in his parkinsonism after the EDTA treatment and discontinuation of the supplement. The abnormal MRI resolved in 3 months. These individuals received 1100 µg Mn/day.

Nelson et al. (1993) evaluated a 44 year old arc welder who welded manganese steel alloy (containing 11-14% Mn) and 20% Mn castings for 25 years indoors without local exhaust ventilation. The worker developed confusion, poor memory, paranoid ideation, difficulty stopping when walking down a slope, and slurred speech. On examination, hyperreflexia of the legs and weakness of his right side was noted. An MRI axial T1 weighted image showed hyperintense signals in the basal ganglia that cleared within 6 months. Neuropsychological testing 8 months after leaving work showed impaired vigilance, recall and learning. He was too clumsy to button his clothes. His urine excretion of Mn was 17 µg/day after treatment with EDTA (normal 0.3 µg/d).

Parkinson's Disease seen after manganese exposure

Racette et al. (2005b) describe a 43 year old alcoholic with liver cirrhosis and portal hypertension for the preceding 4 years, who presented with emotional lability, micrographia, symmetrical rigidity, bradykinesia, postural tremor and postural instability. An MRI showed increased signal density on T1-weighted images in the internal pallidum. Serum ammonia and blood Mn (2.75 µg/dL) were elevated. She was L-dopa responsive with improvement in her gait disorder still present at a 2 year follow-up. A [¹⁸F]fluorodopa PET scan showed reduced uptake in the posterior putamen, consistent with PD except that uptake was only modestly asymmetric.

Manganism in welders

In 1932 Beintker diagnosed manganese poisoning in 2 electric arc welders. At autopsy, there was perivascular degeneration in striatum and pallidum and, to a lesser extent, in the cortex. There was damage in the corpus striatum, putamen and pallidum (Fairhall et al., 1943).

Franek (1994) Evaluated exposures to a welder who had developed classical manganism after 6 years of welding. He did 2 welding tasks. He fabricated steel beams in a shop for structural steel buildings. The Mn content of the steel varied from 0.05 to 2%. The welding shop was unventilated and there was no local exhaust ventilation. Welding was done with GMAW with an argon gas shield. Total Mn levels ranged from 0.032-0.073

mg/m³. He also did outdoor welding of railroad tracks. MMA welding was done with welding consumables containing 2-25% Mn. Mn exposure levels during welding of rail at railroad switches (called frogs, containing 15% Mn) ranged from 4.0-7.2 mg/m³ (equivalent to an 8 hr TWA of 0.032 mg/m³).

Discalzi et al. (2000) describe a case of manganism in a welder. The worker did MMA welding from 1964-1968 and from 1971 to 1998. Mn made up 1.39% of the welding consumables and 0.54% of the steel used. He also worked for 30 years in electrode fixation, a task potentially associated with heavier exposures. Symptoms began in 1996 at the age of 53 with postural tremor, muscular hypertonia and bradykinesia. An MRI showed metal deposition in midbrain and basal ganglia with T1-weighted hyperintense signals in globus pallidus. Urine Mn levels increased from 0.18 to 20.1-27.8 µg/L with each of 3 EDTA treatment courses.

Sato et al. (2000) describe a 56-year-old welder who, after working for 30 years, developed postural instability and writing clumsiness. Neurological findings revealed dystonia of the bilateral shoulders and distal four limbs, masked face, bradykinesia, rigidity, and retropulsion. Brain MRI showed hyperintensity lesions on T1-weighted images in the basal ganglia, cerebral white matter, which reduced in size and density of the globus pallidus. Manganese levels were elevated in both serum (5.0 µg/dL) and urine (2.6 µg/L). Urinary manganese levels increased to 120 µg/L after administration of 2 gm of CaEDTA.

Tanaka and Lieben (1969) studied manganese exposure in 75 Pennsylvania industrial plants. In 12 plants, exposure levels were >5 mg/m³. In the welding and burning of ferromanganese alloy, 11.1% of air samples near welders were >5 mg Mn/m³. 2 of 14 welders had a positive screening exam for manganese effects while one of the two had definite findings of manganism. The latter, a 45 year old manganese burner, first developed symptoms at age 44, one year after beginning work. He had cog-wheeling rigidity, facial masking, infrequent blinking, a monotonous voice, plastic rigidity, difficulty walking backward.

Sadek et al. (2003) evaluated a 33 year old welder 2-3 years after began welding. He welded on a steel-manganese alloy and spent much of his time in a confined ship's hold without wearing a respirator. Symptoms began gradually starting a few months after beginning welding, progressing to the point he was unable to work for the last month before being seen. He had progressive instability of gait, a unilateral tremor more pronounced with intentional activities, cognitive slowing with forgetfulness, inattention, headache, nervousness. On examination he had slow saccadic eye movements, bradykinesia, unilateral cogwheeling rigidity, an expressionless face, monotone speech, and an abnormal gait where he was fast paced, stiff and walking on his toes (cock walk). His serum Mn was 2.29 µg/dL and his urine Mn was 3.1 µg/L. Treatment with L-dopa was ineffective. A T-1 weighted MRI showed hyperintensity of the globus pallidus.

Ono et al. (2002) describe a 17 year old welder who developed myoclonic involuntary movements but not parkinsonism. He had been electric arc welding for 2 years in a plant where manganese was used. On examination he had impairment with finger-nose-finger

movements, dysdiadochokinesia on one side, impaired standing and gait with prominent myoclonic movements of all extremities. Brainstem auditory and somatosensory evoked potentials and an EEG were normal. An MRI showed T1-weighted high intensity signals from the globus pallidus to the cerebral peduncle. He was treated with 2 gm calcium EDTA daily for 5 days associated with an increase in urine Mn from <1 to 30-31 µg/L. By the end of treatment there was marked improvement in his involuntary myoclonic movements. Immediately after treatment, T1-weighted high intensity signals had become less evident and resolved by 3 months after treatment. His blood Mn was 4.3 µg/L (normal 0.8-2.5) decreasing to 2.5 µg/dL immediately after treatment. At a follow-up 3 months later, his blood Mn was 1.6 µg/dL.

Whitlock et al. (1966) evaluated 2 employees at a ferromanganese alloy plant who developed manganism after a process change that required trimming of castings with an air arc burner. In the first case a 54 year old developed forgetfulness, incoordination, unsteady gait, facial masking monotonous voice, increased plastic rigidity of all 4 extremities, symmetrical hyperactive reflexes, wide-based gait with unstable tandem gait, poor rapid alternating movements and a positive Babinski reflex. Urine Mn was 4.58 µg/L increasing to 150 µg/L after EDTA. The second worker developed poor memory, facial masking, decreased associated movements with walking, instability when standing on one leg, slowed alternating and coordinated movements, hyperreactive reflexes and a positive Babinski reflex. There was slight plastic rigidity in all 4 extremities. A urine Mn was 5.48 µg/L increasing to 1000 µg/L with EDTA. Cutting work was done in a 4-sided booth without local exhaust ventilation. Total Mn levels during cutting ranged from 2.3-4.7 mg/m³.

Angle (1995) identified 49 year old railroad shop welder with manganism. The worker had welded, cut and gouged with 18% Mn alloy consumables on 11-15% ferromanganese steel "frogs" for 19 years.

Nelson et al. (1993) describe a 44 year old arc welder working welding manganese steel alloy (containing 11-14% Mn) and 20% Mn castings for 25 years indoors without local exhaust ventilation. He developed confusion, poor memory, paranoid ideation, difficulty stopping when walking down a slope, slurred speech. On examination he was found to have hyperreflexia of the legs and weakness of his right side. An MRI axial T1 weighted image showed hyperintense signals in the basal ganglia that cleared within 6 months. Neuropsychological testing 8 months after leaving work showed impaired vigilance, recall and learning. He was too clumsy to button his clothes. His urine excretion of Mn was 17 µg/day after treatment with EDTA (normal 0.3 µg/d).

Parkinsonism among welders

Kim et al. (1999a) describe an individual who welded for 2 hr/d for 10 years then 10 hrs/d for 2 years. One year before stopping work he developed a tremor, rigidity, masked face, bradykinesia. There was little change with levodopa treatment. A fluorodopa PET scan showed uptake in the left putamen. Treatment with EDTA increased urine Mn excretion from 13.6 to 73.3 µg per day. Blood Mn level 2 months after cessation of exposure was 3.26 µg/dL and urine level was 3.57 µg/L. A shirt that was worn at work for 2 days

contained 40-100 ppm Mn. Total Mn exposures ranged from 0.36-0.86 mg/m³ (mean 0.63 mg/m³) for 5 welders with exposures measured outside of welding shield. Inside shield exposure levels were 51.2 and 70.6% of outside values in 2 workers. The clinical assessment was that the worker had idiopathic PD with superimposed Mn exposure.

Racette et al. (2001; Racette, 2001, Racette and Permultter, 2001) evaluated 15 career welders with PD referred by an attorney. Average age of onset was 46 years, ranging from 29-68 years vs. 63 years among 100 sequential Parkinson's Disease (PD) patients referred to a movement disorders clinic. A family history was positive in 53% of welders vs. 32% of the PD patients. Fluorodopa PET scans of 2 welders showed asymmetric reduced striatal uptake typical of PD. There was no difference in the frequency of psychological symptoms or clinical findings between the welders and PD controls. The lead author pointed out that there was selection bias in this study and a high frequency of a family history PD among the welders. MRIs were normal and showed no evidence of Mn accumulation in the 6 welders who were active at the time of the studies.

Rajput (2001) described a case of parkinsonian syndrome that developed in a welder who had bilateral high T1 signal intensities on MRI of the globus pallidus and substantia nigra. The MRI abnormalities resolved once exposure was stopped. The patient was responsive to L-dopa.

Rasmussen and Jepsen (1987) evaluated 2 cases of parkinsonism that developed in welders at a boiler factory with poor ventilation. One welder, who had worked at the factory for 26 years, developed poor concentration, emotional lability and a tremor at age 47 followed in 4 years by parkinsonian syndrome with bilateral dysmetria and dysidiadochokinesia. The second welder had worked at the factory for 8 years at which time he developed emotional lability and irritability followed in 5 years by parkinsonian syndrome. Prior industrial hygiene surveys of the plant had shown total Mn levels in various jobs to range from 0.02-10.7 mg/m³. Welding was done inside the boiler tanks.

Feldman (1992) included welders in his meta-analysis of 60 case reports of manganese intoxication. Two had tremors that did not respond to L-dopa while the third developed L-dopa responsive PD 30 years after a 30 year working lifetime as a welder.

Kim et al. (2002) evaluated a 48 year old welder who was seen because of an asymmetrical tremor for one year followed by being slow in motion and dysarthria. On a neurological examination there was an asymmetrical postural tremor, bradykinesia, asymmetrical rigidity and a masked face. He did not have difficulty with backward walking or dystonia. There was an excellent response to L-dopa. His blood Mn was 3.06 µg/dL and urine Mn 8.38 µg/L. Among 10 welders at the same workplace, personal total Mn fume exposures ranged from 0.02-2.7 mg/m³ with a mean of 0.28 mg/m³. An MRI showed symmetrical high signal densities to T1-weighted images in the globus pallidus and substantia nigra. A [¹²³I]-β-CIT SPECT study showed decreased binding in striatal regions, most prominent in the caudal part, as seen with idiopathic PD.

Racette et al. (2005a) screened 1423 welders from Alabama who were referred for a medical-legal evaluation. Rigidity was assessed by a movement disorders specialist in a

subgroup of 112 workers. The motor subsection 3 of the Unified Parkinson's Disease Rating Scale (UPDRS3) was assessed using a standardized video examination. 48 subjects were also rated in person. Specificity of the video rating system was 91-100% with a sensitivity of 56%. The authors assumed screening identified all cases of PD among Alabama welders and that the total number of welders fell within the SOC codes for welders, welder helpers and boilermakers. They adjusted the numbers reflected by the SOC codes for the age distribution of the studied population, 40-49, 50-59, 60-69. 148 subjects were diagnosed as definite PD, 185 as probable and 1000 as unclassified. Common features in the latter group included isolated bradykinesia (96%), isolated postural or action tremors (6.7%), and bradykinesia with postural instability (19%). There was no significant relationship between total welding hours and UPDRS3 score nor diagnosis of PD and welding hours based on odds ratios, though a regression analysis (data not presented) showed a relationship. When age was added to the model, only age was found to be significantly associated with diagnosis of PD. The distribution of cases by age was as follows:

	<u>#definite</u>	<u>#definite + probable</u>
40-49	44	100
50-59	71	161
60-69	53	119

The authors further compared age-adjusted prevalence (with above assumptions) of PD with prevalence of PD in Covich County, MS. Odds ratios ranged from 7.6-10.33 depending on whether conservative or liberal criteria for diagnosis were used. The authors assumed that they had only screened 12% of active welders in Alabama. They felt that the findings of isolated, mild bradykinesia and postural tremors could be consistent with pre-clinical effects of manganese exposures. They felt that the strong association between age and diagnosis of PD in this younger population may support their previous study (Racette et al., 2001) which found an earlier age of onset of career welders with PD. This study does have some design weaknesses that limit the strength of its conclusions. As with the previous study (Racette et al., 2001), there is likely a selection bias. Further, the study likely underestimated population of welders by a factor of 5 since the neglected workers who weld but are not classified as welders in determining the total number of workers exposed to welding fume in the state of Alabama: with an increase in the number of potentially exposed subjects, the calculated odds ratios would be similarly reduced by a factor of 5 (US Department of Labor, 2000). Although the authors did not give the age of onset or overall mean age, one can calculate mean age for definite PD using liberal criteria as 58.1 years. This age is similar to other "selected" populations, i.e., those referred to movement disorders clinics (Pezzoli et al., 2000).

Studies of Parkinson Disease patients have not supported a relationship between welding and PD. Goldman et al. (2004) investigated whether or not young age of onset of PD was associated with a history of working as a welder. The authors had information on the primary occupation for 885 PD patients seen at a movement disorders clinic. 3% were construction workers and 0.2% were welders. 122 of the 885 PD patients had an onset of ≤ 50 years of age and early age of onset was not significantly related to welding or construction work.

Semchuk et al. (1993) evaluated 130 PD patients from various clinics and neurologist's practices and matched each with 2 randomly-selected community controls. The mean age of symptom onset was 58.0 ± 12.2 years. 9.1% of the cases were diagnosed before the age of 40. Cases and controls did not differ in the previous work-related exposures to manganese.

Olanow (2004) noted that he had completed a chart review of approximately 1500 PD patients performed at 3 major PD centers in different geographical areas. Only 1 patient noted that he had been working as a welder at the time of diagnosis and none reported welding as a major lifetime profession.

Noonan et al. (2002) developed a case-referent set based on the mention of PD in the death certificates of men dying in Colorado between 1987 and 1996. A total of 1477 cases were identified. There were 1477 referents. There were 12 welders in the PD group and 6 in the referent group for an OR of 2.26 (not significant).

Gorell et al. (1997) identified idiopathic Parkinson's disease (PD) patients 50 years or older from 239,722 patients seen at a Henry Ford Health System clinics between 1988 and 1992. 1243 patients were coded with having PD. Medical record reviews were conducted on the 865 who were still in the area, alive and under care identified 232 who did not have secondary causes of parkinsonism and had a clear diagnosis of PD. These were age, race and sex matched with 970 population controls of whom 144 cases and 464 controls agreed to participate in the study. The ratio of men in the 50-59 age category to that in the 60-69 age category was 1:4.6. Among cases, 2.1% had had Mn exposures lasting >20 years vs. 0.2% of controls (OR = 10.61, 95% CI = 1.06, 105.83). However, among the 5 workers with Mn exposures, 4 were also exposed to lead, an exposure the authors identified as a risk factor for PD. No welders were included in the study. Gorell et al. (1999a) further evaluated this data set in a logistic regression model. Manganese dropped out as a significant variable leaving smoking, family history of PD and exposure to insecticides or lead/copper as significant variables. In a further logistic regression analysis of this data set the authors (Gorell et al., 2004) did not identify welding as a significant exposure variable. They also found that if they had relied on either a job exposure matrix or self-report alone in the original case-control study, there was no significant association between PD and manganese exposure.

Tanner et al. (2003) reviewed occupations of PD patients and found no evidence that welding increased risk of PD. They took lifelong occupational histories of twin pairs discordant for PD. 96 pairs were included in the study. 8 twins with PD had a history of welding and 8 without PD had been welders for and odds ratio of 1.0.

Witholt et al. (2000) used a rodent model to see whether or not Mn exposures could result in neurobehavioral changes where there is striatal damage, such as seen in PD. They unilaterally injected the striatum of rats with 6-hydroxydopamine (6-OHDA) with resultant depletion of striatal dopamine by 60-70% (secondary to cell loss) but without neurobehavioral changes. Behavioral changes are usually not seen in this model until 80% dopamine depletion. Rats were treated with Mn intraperitoneally at dose levels of 4.8 mg/kg, 3 times a week for 5 weeks (a total of 72 mg/kg). Mn treatment without 6-OHDA

did not result in striatal dopamine depletion nor increased dopamine depletion with 6-OHDA pre-treatment. Mn exposure increased whole brain Mn levels 3.4 fold. Without 6-OHDA treatment, Mn exposure was associated with behavioral changes, including gait abnormalities, impaired balance and decreased arousal. Few additional changes were seen when Mn was given to 6-OHDA pre-treated rats in those tests that tested the bilateral function of the basal ganglia but showed interactive effects on some (but not all) tests that were sensitive to unilateral basal ganglia function. The authors conclude that Mn exposure may increase the risk of neurobehavioral impairment in subpopulations with a pre-parkinsonism state.

Parkinsonian syndrome and carbon monoxide exposure

Exposures to welding fume also result in exposures to excessive levels of carbon monoxide when air-arc gauging with carbon or graphite electrodes or when CO₂-shielded MAG welding is conducted in poorly ventilated areas (Sjogren, 1994). Acute, high exposures to this toxin can cause damage to the basal ganglia and a parkinsonian syndrome. With a parkinsonian syndrome after acute CO poisoning, damage affects the globus pallidus rather than the substantia nigra. CO exposure results in impaired oxidative metabolism and induces free radical formation in the brain, particularly in the basal ganglia (Riedl et al., 1999).

Choi (2002) evaluated 242 cases of acute CO poisoning. 9.5% developed a parkinsonian syndrome. Resting tremor was not seen. L-dopa was ineffective. Of the 16 patients re-evaluated 1 year after exposure, 81.3% had recovered within 6 months. In another study, Choi and Cheon (1994) found that among 242 patients with CO poisoning, movement disorders were found in 13.2%. Among the affected group, 71.9% had parkinsonism and 15.6% had dystonia. Mimura et al. (1999) examined 156 institutionalized patients 33 years after a CO poisoning incident. Their mean age was 69.2 years. 21.8% had extrapyramidal findings including in 4.5%, tremor in 10.9%, and muscle rigidity in 16%. Pallidum lesions were found on MRI in 37.9%.

Although acute CO poisoning and PD have not been described in welders, one epidemiological study suggests a possible relationship between chronic CO exposure and PD. Seidler et al. (1996) evaluated 380 Parkinson's Disease patients recruited from 9 German neurological clinics and compared exposure factors to 379 neighborhood and 376 regional controls. Mean age at onset of symptoms was 50.5 ± 7.2 years. Patients reported more free time or occupational exposure to CO and exhaust fumes (odds ratio significant with a confidence interval of 1.2-2.4).

Lowest and no effect levels for manganism in man

Overt manganism has been seen with inhalation exposures ranging from 2-22 mg total Mn/m³ (WHO, 2000). Feldman (1992) conducted a meta-analysis of 60 individual case reports of manganism and population studies of 325 workers and control subjects. 72% had exposure measurements of Mn in air, blood and/or urine. 6% of 117 workers with exposures >5 mg/m³ had acute extrapyramidal features. Tremor occurred in 24 of 60. Among exposed symptomatic cases, 15% fit the published criteria for PD while parkinsonian syndrome accounted for 85%. Table 2 summarizes exposure levels where manganism has occurred (as well as where manganism is prevented).

Flinn et al. (1940) evaluated 34 men exposed to Mn at an ore-crushing mill and compared the findings to 16 men without Mn exposures working at an adjacent chrome ore processing plant. Exposures ranged from 10.4-173 mg/m³. Manganism symptoms occurred only in workers exposed to >30 mg/m³. Workers were exposed for an average of 5.26 years. Mn levels were elevated in the lungs in one worker who had not been exposed for 7 years. 11 workers had manganism with findings of tremors, gait and speech disturbances, muscular weakness, facial masking. Urine Mn levels among workers ranged from 4-48 µg/L with increased levels found in 3 workers not exposed for 7-19 years.

Wyntner (1962) saw cases of manganism develop among about 200 miners after the introduction of dry drilling. Drilling procedures were changed and the ventilation system was improved so that Mn levels in mine decreased to 0.19-0.42 mg/m³. With these changes, no new cases developed during the next 9 years.

Kim et al. (1999) evaluated workers exposed to Mn during welding (34), smelting (39) and welding rod manufacturing (16) as well as 35 controls. Mean exposures to welders was 0.53 (range 0.1-1.56) mg/m³, to smelter workers 0.14 (range 0.08-1.4) mg/m³, and welding rod manufacturing workers 0.15 (range 0.02-0.42) mg/m³. Enhanced signals were found in 73.5% of welders, 41% of smelter workers and 0% of welding rod manufacturing workers. No signs of rigidity, bradykinesia or walking problems were observed during 6 months of follow-up. Neurological examinations showed no signs of manganism. Some postural tremors were seen but the incidence was not different between groups.

Saric et al. (1977) evaluated 369 ferroalloy production workers exposed to 0.301-442 mg/m³ Mn. For most the average exposure was about 11 years. The one worker felt to have manganism had been exposed to 5-16 mg/m³ of Mn over a period of >20 years.

Smyth et al. (1973) evaluated exposures and clinical effects in a ferromanganese alloy production and processing. The highest exposures were seen with ore crushing and screening in the screening plant with exposures ranged from 8.2-80 mg/m³ with an average of 35.0 mg/m³ in the breathing zone of operators and helpers prior to 1961. In 1961 there was improved ventilation with a decrease in Mn exposures. When measured at the time of the study (ca. 1965), exposures to screening plant operators and helpers averaged 6.3-12.9 mg/m³. In the production facility, Mn levels averaged 0.12-3.60 mg/m³. At the pig casting machine, average exposures ranged from 4.4-13.0 mg/m³. A neurologist evaluated the 142 employees: 3 exposed to fume and 2 exposed to dust had symptoms and findings of manganism. The 2 with dust exposures had worked for 23 years as screening plant operators and helpers. Two of the symptomatic fume-exposed workers had worked at the pig iron casting machine with the third working as a hot blastman (average exposure 0.33 mg/m³). All subjects were still working and one also maintained a farm. Symptoms and findings ranged from loss of associative arm movements when walking as the only finding in 2 workers to masked facies, absent associative arm movements when walking, resting tremor, cogwheel rigidity and micrographia in 3 workers.

Zheng et al. (2002) evaluated welders and smelterers at ferromanganese metallurgical factories who had developed manganism. Findings included cogwheel rigidity, dystonia,

tremor, muscle weakness, whispering speech, facial masking and gait disturbances. Mn exposures ranged from 0.06-7.8 mg/m³ with a median exposure level of 3.9 mg/m³. A total of 49 cases were assessed, 30 with <20 years of exposure and 19 with >20 years of exposure (averaging 18.4 yrs). 65.3% were <43 years old at the time of evaluation.

Wang et al. (1989) evaluated 132 workers at a ferromanganese smelting plant where a case of manganism had occurred. The highest exposure area averaged 28.8 mg/m³. Other exposures ranged from 0.1-1.5 mg/m³. 6/8 workers with high level exposures for 8 months developed manganism. When the ventilation was repaired so that maximum levels were now 4.4 mg/m³, no new cases developed during the next 4 years. Blood Mn levels increased with increasing exposure being 1.49 µg/dL in controls and 14.6 µg/dL in the high exposed group. Individuals exposed to 0.5-1.5 mg/m³ averaged 3.13 µg/dL and those exposed to 0.1 mg/m³ averaged 2.52 µg/dL.

Sabnis et al. (1966) evaluated workers at a ferromanganese alloy factory. Daily average weighted exposures were <2.3 mg/m³ for all workers with maximum levels reaching 10 mg/m³. No cases of manganism were observed. However, no clinical examinations were performed. Manganese poisoning occurred at a nearby factory where exposures ranged from 8.4-8.8 mg/m³ in operations where comparable values in their plant ranged from 2.3-2.7 mg/m³.

Emara et al. (1971) evaluated 36 workers exposed to MnO₂-containing dust in a dry battery manufacturing plant. Mn exposures averaged from 3.0-18.0 mg/m³. 8 workers showed evidence of chronic Mn poisoning. Mn blood levels averaged 0.03 µg/dL in the 6 workers no longer exposed to MnO₂ and 1.7 and 2.3 µg/dL in the 2 workers with continued exposure. 6 were psychotic, one had Parkinson's Disease (age 30) and one had choreo-athetosis. Among the 8, 6 had headaches, memory disturbances and sleepiness, 5 had uncontrollable laughter and aggressiveness. 3 had impotence and impulsive acts (running, dancing, singing and uncontrolled talking) and inability to prevent falling with forced movements and 2 had uncontrolled weeping, irritability or depression, euphoria and hallucinations.

Lowest and no effect levels for manganism in experimental animals

Exposures can occur in animal models to levels as high as 3000 µg/m³ without detectable brain effects. Griffin et al. (1978) exposed rats for 8 weeks and monkeys for 1 year for 23 hr/d to 100 µg/m³ of particulate Mn as Mn₂O₃ (combustion of methyl cyclopentadienyl manganese tricarbonyl). Mn levels increased in soft tissues, including brain. No gross or microscopic changes of any tissues attributable to Mn exposure. No signs of toxicity or changes in clinical parameters during study.

Ulrich et al. (1979a,b) exposed rats and monkeys to Mn₃O₄ (manganese tetraoxide) at levels of 11.6-1152 µg Mn/m³ continuously for 9 months. There were no exposure-related clinical signs and no Mn-related microscopic changes of the brain. With this exposure regime, they found no limb tremor or EMG abnormalities, findings seen in workers or experimental animals with excessive Mn exposures.

Normandin et al. (2000) exposed rats for 30 hrs/week to Mn phosphate at levels ranging from 300-3000 $\mu\text{g Mn/m}^3$ for 13 weeks. No signs of brain pathology were found, including degenerating neurons or astrocyte changes, in the globus pallidus, caudate nucleus or putamen of treated rats. There were no changes in tremor power or frequency and no neurobehavioral changes.

Rhesus monkeys were exposed to MnO_2 dust at concentrations of 0.7 and 3.0 mg/m^3 , 22 hours/day for 10 months. 2/3 monkeys at the higher exposure level developed mild tremors, loss of dexterity, loss of pinch force starting 3-4 months into exposure. No effects were seen at the lower exposure (438 $\mu\text{g/m}^3$; AWS, 1981).

Table 2: summary of exposure levels associated with manganism in man

Activity	NOEL* (mg/m^3)	LOEL* (mg/m^3)	Reference
Mn ore crushing	10.4-30	47 (average)	Flinn et al., 1940
Mn ore mining		>5 1/3 rd of time	Schuler et al., 1957
Mn ore mining	0.19-0.42		Wyntner, 1962
Industrial plants/welding		>5	Tanaka & Lieben, 1969
Industrial plants/welding	0.14-0.53		Kim et al., 1999
Steel workers		Average 3.5 (range 2.3-4.7)	Whitlock et al., 1966
Ferroalloy worker		5-16 x 20 years	Saric et al., 1977
Ferromanganese alloy production		8.2-80; 4.4-13; 0.33	Smyth et al., 1973
Ferromanganese metallurgical plants		3.9 (median)	Zheng et al., 2002
ferromanganese smelting plant	4.4	28.8	Wang et al., 1989
ferromanganese alloy factory	<2.3	8.4-8.8	Sabnis et al., 1966
Dry battery manufacturing plant		3-18	Emara et al., 1971

*NOEL = no effect level. LOEL = lowest effect level

V. Pre-clinical effects of excessive exposures to manganese

Neurophysiological effects with low-level manganese exposure

Low level exposures to Mn can result in neuropsychological changes with few or none of the neurological changes seen with manganism. The performance of Mn workers is less precise and effective in tasks that require coordinated, sequential, alternating movements at high speed, functions regulated by extrapyramidal system. With environmental exposures to low levels of Mn one sees decreased ability to perform regular, rapid and

precise pointing movements and to obtain high maximum rotation speed in alternating movements.(Lucchini et al., 1999).

Roels et al. (1985, 1987a,b) described their evaluation of 141 workers in a Mn salts and oxide production plant. Subjects were exposed to an median of 0.97 mg/m^3 of Mn for an average of 7.1 years. Blood Mn averaged $1.36 \text{ }\mu\text{g/dL}$ (levels in controls average $0.57 \text{ }\mu\text{g/dL}$) and urine averaged $4.76 \text{ }\mu\text{g/g}$ creatinine (control values averaged $0.30 \text{ }\mu\text{g/g}$ creatinine). Production began in 1964 with no environmentally significant changes to the plant since that time. However, production of MnO_2 increased systematically from 2800 mt in 1970 to 22000 mt in 1981 without concomitant improvements in ventilation. A single, blind neurological examination was conducted to detect early signs of parkinsonism including rigidity, cog-wheeling, balance, tremor, drawing, and mask-like facies. There were more smokers among the Mn-exposed population. Except for trunk rigidity, no significant differences were identified on these examinations between exposed and control groups. There was no statistically significant relationship between individual blood Mn or urine Mn values and any test result. However, when workers were divided into 6 groups based on ranges of blood Mn or ranges of exposure, eye-hand coordination and hand steadiness, but not simple reaction time or short-term memory, were related to blood Mn. The prevalence of abnormal scores varied from 11 to 19% vs. 2 to 5% in controls.

Saric et al. (1977) evaluated 369 ferroalloy production workers exposed to $0.301\text{-}442 \text{ mg/m}^3$ Mn. For most the average exposure duration was about 11 years. On a neurological exam, Mn-exposed workers had an incidence of 11.5-14.2% resting tremor. Cogwheeling rigidity combined with resting tremor was seen in one worker. Among a control population (working in the electrode facility of the plant), resting tremor was seen in 5% of 190 workers but none had a combination of resting tremor and rigidity. This group was exposed to $2\text{-}30 \text{ }\mu\text{g/m}^3$ of Mn.

Beuter et al. (1994) examined 10 former ferro- and silico-manganese alloy plant workers. The subjects had worked for an average of 13.9 years of exposure. But there had been a 12 month interval since their last exposure. Measurements of rapid hand movements were made with a diadochokinesimeter in the past-exposed group, a control group without exposure to manganese and PD patients. Differences were not noticeable at natural cadences between subjects and controls but when asked to move their hands as fast as possible, differences became apparent. Both workers and patients had asymmetries in performance between the right and left hands.

Lucchini et al. (1999) performed neuropsychological testing on 61 ferroalloy workers and 87 controls. Total Mn exposures in 1981 ranged from $0.167\text{-}1.597 \text{ mg/m}^3$. By 1997 exposures had decreased with average total Mn exposures ranging from $0.055\text{-}0.256 \text{ mg/m}^3$. The overall lifetime average exposure of workers was 0.079 mg/m^3 with a lifetime cumulative exposures averaged $1.20 \text{ mg/m}^3\text{-yr}$ with an average length of exposure of 15.17 years. Significant improvement in air levels were associated with improved ventilation in 1988-9. A previous study of same workers in 1995 showed abnormalities (addition, digit-span, finger tapping, symbol digit) in high level exposed workers. Effects of shift work and blood lead levels were controlled for in the analysis. No differences

were found in reaction times and in tests of coordination (hand pronation-supination). There was a higher tremor frequency but amplitude and harmonics were no different between exposed and controls. Digit-span and addition were more affected in Mn workers. A comparison of results of SPES tests (symbol digit, finger tapping, digit span) in 30 workers tested in 1990-1 and in the present study did not show any differences. The authors found a correlation between digit span, finger tapping and symbol digit results and the cumulative exposure index. There were no differences in average visual contrast sensitivity at different frequencies between exposed and control workers. There was an increased frequency of symptoms of irritability, equilibrium loss and rigidity, similar to symptoms found in other studies.

Iregren (1990) and Wennberg et al. (1991) report on a study of foundry workers exposed to Mn. The 15 most exposed workers at each of 2 Swedish foundries were recruited. Present exposures averaged 0.25 mg/m^3 with an average exposure of 0.18 mg/m^3 at one smelter and 0.41 mg/m^3 at the 2nd. Respirable Mn levels ranged from 20-80% of total Mn levels. The mean duration of exposure was 9.9 years. Earlier exposure data was available for each foundry: there had been no changes in exposure patterns over the previous 17-18 years. A reference group of 60 workers was chosen from a steelworks and mechanical industry without Mn exposures. Each exposed worker was matched to 2 controls based on age, geographic area and type of work. EEG changes were not increased significantly. There were longer auditory evoked potential latencies with exposure but no statistically significant changes in brain stem evoked potentials. On neuropsychological testing, significant differences were found between the 2 groups for simple reaction time, tapping speed, additions, verbal ability and digit span. Differences in vocabulary reflect differences in cognitive function of the 2 groups and the differences were felt not likely to be related to Mn exposure. When controlling for vocabulary differences, the 2 groups were found to be similar for additions but continued to be significantly different for the psychomotor tests. These changes were not related to the number of years of exposure or measures of exposure to total Mn. Abnormalities in some neuropsychological measures (simple reaction time, digit span, and mood) correlated to respirable Mn exposures.

Chia et al. (1993) studied workers at 2 Singapore Mn ore milling factories with greater than 1 year exposure with an average of 7.4 years exposure and with 71% of workers with at least 5 years of exposure. From 1981 to 1991 the mean level of exposure to total Mn was 1.59 mg/m^3 (dropping from 6 mg/m^3 in 1981 to 0.05 mg/m^3 in 1991 with a mean air level of 4.16 mg/m^3 in 1983 and 0.99 mg/m^3 in 1986). There were significant increases in frequency of insomnia among workers but no significant differences in sensory and motor conduction. The exposed group did poorly in all neurobehavioral tests including the Santa Ana test, finger tapping, digit span, digit symbol, Benton visual retention, pursuit aiming and trail making, suggesting some degree of motor dysfunction. Hand-eye coordination was poorer in exposed group. Exposed workers did not have clinical signs of Parkinson's Disease and no findings of parkinsonism on a standard neurological examination.

Brown et al. (1991) examined refinery workers exposed to Mn dust. There were no controls but they compared workers with high and low Mn exposures. The cutoff between high and low exposures in this study was 5 mg/m^3 . The low exposure group had an average exposure of 0.81 mg/m^3 for 11.2 years while high exposure group had an average

Mn exposure of 10.58 mg/m^3 for 12.61 years. There was no evidence of manganese changes on neurological examinations of workers in either group. Neuropsychological studies found no differences in digit span, configural memory (digit symbol substitution and geometric design memory), sensorimotor function (grooved pegboard test) or visuomotor function (digit symbol) between groups. There were minor differences in verbal memory.

Gibbs et al. (1999) describe a medical monitoring program that was established in 1992 for the evaluation of workers with Mn exposures at a metal producing plant. The program included yearly testing of finger tapping speed, complex reaction time, hand tremor and hand dynamometry. Analysis of this data in 1994 and 1995 did not show any differences between employees in Mn processing areas and those in other areas. 75 Mn workers were matched to unexposed controls. Measurements were made of hand steadiness, hand-eye coordination, choice reaction time, finger tapping, tremor, memory, concentration and mood. Equipment used was functionally identical to that used by Roels et al. (1992). Results were compared to average and cumulative exposures to respirable and total Mn. For total Mn, average exposure was 0.18 mg/m^3 , the geometric mean exposure was 0.11 mg/m^3 and a lifetime geometric mean exposure of 1.5 mg-yr/m^3 . For respirable dust the average exposure was 0.066 mg/m^3 with a geometric mean of 0.036 mg/m^3 and lifetime geometric mean of 1.5 mg-yr/m^3 . For comparison, Roels et al. (1992) found total Mn exposures in their study averaging 1.8 mg/m^3 with a geometric mean exposure of 0.095 mg/m^3 and lifetime geometric mean 3.5 mg-yr/m^3 . For respirable Mn exposures, Roels et al. found an average Mn exposure of 0.30 mg-yr/m^3 with a geometric mean of 0.22 mg/m^3 and a lifetime geometric mean 0.79 mg-yr/m^3 . Exposures also compare with the Lucchini et al. (1995) who found geometric mean lifetime integrated respirable Mn exposures ranging from 0.18 to 0.67 mg-yr/m^3 . While both Roels et al. (1992) and Lucchini et al. (1995) found exposure-related effects, the authors of this study found no neurobehavioral abnormalities among their subjects.

Mergler et al. (1994) evaluated 115 workers at a ferromanganese and silicomanganese alloy facility. Controls were workers at neighborhood plants without neurotoxic exposures with 74 paired for age, education and smoking. Average exposure was for 16.7 years. Stationary sampling for total and respirable Mn was taken at 13 locations. Mean total Mn was 1.186 mg/m^3 with a geometric mean of 0.225 mg/m^3 . Mean respirable Mn was 0.122 mg/m^3 with a geometric mean of 0.035 mg/m^3 . Urinary Mn was similar between controls and workers but blood Mn levels were slightly higher with exposure (mean $1.12 \text{ } \mu\text{g/dL}$ exposed, 0.72 $1.12 \text{ } \mu\text{g/dL}$ controls). Neurophysiological tests were not significantly different between exposed and controls for finger tapping, simple reaction time, hand strength, attention, concentration and memory. Exposed workers had more symptoms of fatigue, sleep disturbances and adverse emotional state and findings of tremor, difficulties with motor functions requiring coordinated, sequential, alternating rapid movements and cognitive flexibility, motor functions mediated by the extrapyramidal system, and enhanced smell perception. Scoring on the Luria Nebraska Neuropsychological Test Battery, which discriminates between neurological patients and controls, showed an absence of clinical neurological disorders. Neuromotor slowing was evident on graphomotor tasks. Exposed workers were no different than controls on tests of intellectual function but had difficulties with cognitive flexibility and set shifting.

Wennberg et al. (1992) evaluated 30 workers at a steel smelting works with a minimum of 1 year of work. Mn levels in work areas ranged from 0.03-1.62 mg/m³ with mean values of 0.18 mg/m³ at one smelter and 0.41 mg/m³ at the other. Results of neurophysiological tests were compared with 60 age-matched controls from nearby industries without Mn exposures. There were no differences in EEG, brainstem evoked potentials or auditory evoked potentials. There was impaired ability to do rapid alternating movements.

Mergler et al. (1999) evaluated people living near a former manganese alloy production plant. They identified problems with tremor (pointing task), acquisition, delayed recall, visual recognition, digit span, and dysdiadochokinesia in the overall population. In individuals with blood Mn \geq 0.75 μ g/dL, delayed recall, learning and acquisition were worse than in those with values lower than 0.75 μ g/dL while no dose-response was seen with visual reproduction.

Kaji et al. (1993) found no correlation between measurements of postural sway and either blood or urine Mn levels in a study of 66 workers at a Mn refinery. Mn exposures ranged from 0.02-0.46 mg/m³ with workers working for an average of 22.6 years. Blood Mn values ranged from 1.91-2.69 μ g/dL (controls 1.78 \pm 0.52 μ g/dL) and urine Mn values ranged from 2.60-4.22 μ g/gm creatinine (controls geometric mean of 1.16 \pm 1.93 μ g/gm creatinine).

Lucchini et al. (1997) evaluated 35 of 39 furnace and casting workers at a ferromanganese alloy product plant who were exposed to manganese oxides. The average duration of exposure was 14.5 years. The respirable fraction of the manganese particles was 50-60%. Mn exposures decreased from 1987-8 (when exposure measurements were first available) because of major process and ventilation changes. Total and respirable dust levels were determined by stationary sampling. A cumulative exposure was determined based on current job-specific exposure levels and number of years spent at each job. Workers were tested for eye-hand coordination. Total Mn levels ranged from 0.026-0.750 mg/m³ with an average of 0.093 mg/m³ and a geometric mean of 0.193 mg/m³. There was an excellent relationship between log blood Mn and log cumulative exposure index ($r = 0.52$, $p < 0.002$). Hand-eye coordination (aiming pursuit) deteriorated with increasing blood Mn levels with an $r = 0.36$, $p < 0.05$. Blood Mn among exposed workers had a geometric mean of 0.98 μ g/dL vs. 0.68 μ g/dL in the control group. Urine Mn levels had a geometric mean of 3.0 μ g/L in exposed workers vs. 0.43 μ g/L in the control population. There were no relationships between aiming pursuit scores and age, alcohol consumption or education. Smoking frequency was not significantly different in exposed vs. control workers.

Roels et al. (1992) evaluated 92 Mn exposed workers at a dry alkaline battery plant with a total work force of 1100 workers of whom 102 were currently exposed to Mn. Findings were compared to those of 101 age-match controls not exposed to neurotoxic chemicals. They used a Casella cyclone to collect total and respirable dust. The average duration of exposure was 5.3 years. Exposed workers had similar smoking histories to those of controls. The authors found no correlation between blood Mn or urine Mn and various exposure parameters. When they divided the workplace into 6 exposure categories, there was an excellent correlation between mean air values and geometric mean urine values ($r = 0.83$, $p < 0.05$). On the average respirable Mn was 25% of total Mn. Geometric mean

lifetime exposures (assuming current exposure were the same as in the past) were 0.795 mg-yr/m³ for respirable Mn and 3.505 mg-yr/m³ for total Mn. There were no differences in neuropsychological complaints between control and Mn groups. There was a significant difference in reaction times, hand steadiness (tremor) and eye-hand coordination between exposed and control groups. Short term memory was similar in each group. Eye-hand coordination was significantly different from controls for cumulative exposure indexes (CEI) of respirable Mn of <0.600 mg-yr/m³ (low exposure group) and greater. For simple visual reaction time and hand steadiness (tremor), differences were significant in the exposure group with >1.200 mg-yr/m³ respirable Mn exposure with no significant differences at 0.600-1.200 mg-yr/m³. Similar relationships were found with total Mn.

Deschamps et al. (2001) evaluated 114 workers with at least 6 months of exposure to MnO₂ at an enamels production company. Total respirable Mn exposures averaged 0.057 mg/m³ in personal samples and 0.013 mg/m³ in area samples. The mean duration of exposure to Mn was 19.87 years. There had been no changes in production volume, production process or ventilation system during the past 20 years. Workers were matched with unexposed workers for age, educational level and ethnicity. Smoking habits did not differ between exposed and control workers. Each individual was examined for early neurological signs of parkinsonism including rigidity, hand oscillation, balancing and tremor. Psychomotor studies were chosen to assess domains of speech regulation and initiation, attention, concentration, memory, cognitive flexibility and affect. No cases of possible or probable parkinsonism were identified. No cases had tremor while one control had a tremor during writing. There were no significant differences in performance on psychomotor tests between exposed workers and controls. Regression analysis showed no significant relationship between length of employment and blood Mn.

Lucchini et al. (1995) evaluated 58 ferromanganese alloy plant workers 1-42 days after their last exposure. 19 were furnace workers, 19 maintenance workers with moderate exposures and the remainder in low exposure areas. During the preceding 10 years, total Mn levels had decreased from a geometric mean of 1.59 mg/m³ to a geometric mean of 0.270 mg/m³ in the furnace area, from a geometric mean of 0.319 to 0.124 mg/m³ in the maintenance area and from a geometric mean of 0.070 to 0.027 mg/m³ in the service areas. Average respirable Mn exposures per year, based on area samples, were 13.7, 16.8 and 48.4 µg/m³ in the low, medium and high exposure groups. Workers in the high exposure group had poorer performance on tests of additions, symbol digit, finger tapping and digit span than the medium or low exposure groups. Simple reaction time was no different between groups. There was no relationship between performance and years of exposure.

Hua and Huang (1991) evaluated 17 ferromanganese alloy factory workers who had been exposed to > 2mg/m³ Mn for an average of 11.88 years. Results were compared with patients with manganism or Parkinson's Disease (PD). Brainstem evoked potential studies and computerized tomography scans of the brain were normal. Workers and controls received full neuropsychological evaluations including finger tapping and the Purdue pegboard test. In none of the tests were exposed workers significantly different from the control group. In contrast manganism patients had impairments in intellectual functioning,

visual discrimination of unfamiliar faces, manual dexterity, and information processing speed while motor speed, learning, visual attention, and memory were normal.

Crump and Rousseau (1999) have used the same neurophysiological studies as conducted by Roels et al. (1985, 1987) to monitor workers at the same Mn oxide and Mn salt producing plant as studied by Roels et al.. Tests included those assessing short-term memory capacity, eye-hand coordination, hand steadiness, and visual reaction time. After controlling for age and year of testing, reduced hand steadiness was significantly associated with blood Mn and (marginally) urine Mn, and both reaction time and one measure of hand steadiness were significantly associated with years of Mn exposure. No significant associations were found between any measure of Mn exposure and results from either short-term memory or eye-hand coordination tests.

Neurophysiological effects among welders

Barrington et al. (1998) evaluated 4 welders and 2 machinists at a ferromanganese alloy plant for autonomic dysfunction. Sampling during welding found air levels ranging from 0.0035 to 4.29 mg/m³ with 8 hr TWA levels ranging from 0.08-1.364 mg/m³ (average 0.46 mg/m³ with calculated 8 hr TWA inside welding hood of 0.44 mg/m³). Gross neurological abnormalities were not found except in an index case of manganese. Symptoms among workers included irritability, headache, sleep disturbances, decreased memory and concentration, dizziness, and anxiety/depression. On neuropsychological testing, memory and attention were impaired in 2/6 (including index case of manganese) with minor deficits in the others attributed to mood changes. RR interval was shorter and RR variability was greater than in control subjects. In the 5 frog shop workers abnormalities reflecting loss of parasympathetic tone were seen.

Bowler et al. (2003) performed neuropsychological testing on 76 current and former steel welders, averaging 24.9 years of exposure, and on 42 unexposed control workers. There were no differences in tests of verbal skills, verbal retention and auditory memory. Welders performed worse on tests of verbal learning, working memory, cognitive flexibility, visuomotor processing speed and motor efficiency.

Sjogren et al. (1996) evaluated 202 railroad track welders with >5 years exposure. 13 had welded a high manganese alloy steel used at crossings for >100 hours. Controls were exposed for 2-8% Mn in fumes from the electrodes used for regular track welding. Workers were evaluated with Swedish performance evaluation system (SPES) and 3 manual tests. Testing included assessments of simple reaction time, finger tapping speed, finger tapping endurance, digit span, vocabulary, tracking (eye hand coordination), symbol digit, the Luria Nebraska motor scale, diadochokinesometry, and brainstem and auditory evoked potentials. High exposed welders had more sensory and motor symptoms and sleep disturbances than controls. Neurobehavioral studies were no different from controls except for differences in motor function including tapping speed, the Luria Nebraska motor scale, and pegboard speed and accuracy. There was prolonged auditory evoked potential latency in Mn-exposed welders. Brainstem evoked potentials were no different between exposed and control welders as were tests of dysdiadochokinesia.

26 of 323 welders given a symptom survey complained of dizziness. Rudell et al. (1988) evaluated 7 of the welders who complained of dizziness, 7 welders without dizziness symptoms and 25 controls. Tests of saccadic and smooth pursuit eye movements were conducted before and after 30 minutes of manual arc welding (mild steel and stainless steel), metal active gas welding (with 20% CO₂ in the shield gas) or metal inert gas welding. Welding was done without local exhaust ventilation. Total Mn levels inside the welding shields averaged 1.1 ± 1.6 mg/m³. (0.074 for GMAW; 0.066-0.50 for MAG; 0.80-4.88 for MMA on mild steel and 0.126 for MMA on stainless steel). CO was not measured. 4 symptomatic welders and 2 asymptomatic welders had worse scores for smooth pursuit after welding. Welders as a whole had baseline values for smooth pursuit that were impaired compared to controls. Saccadic eye movements were normal. Oculomotor function impairment after welding bore no dose-response relationship to Mn or any other measured particulate.

Sinczuk-Walczak et al. (2001) evaluated 62 welders and fitters. Air Mn levels during welding averaged 0.399 mg/m³ with a geometric mean of 0.154 mg/m³. The authors also examined 13 workers exposed to Mn dust during battery production with similar exposures to that of the welders. Standardized examinations were conducted that included evaluations of tremor, movement disorders and dysidiadochokinesia. Exposed workers had symptoms of emotional irritability, concentration difficulties, sleepiness and paresthesias. Symptoms did not correlate with either current or cumulative Mn exposures. Neurological examinations did not disclose focal changes or grounds for diagnosing toxic encephalopathy. There were no differences in EEGs between exposed and controls. Visual evoked potential changes did not correlate with current exposure but did correlate with cumulative Mn exposure.

Carbon monoxide exposures and pre-clinical neuropsychological and neuropsychological effects

Just as high-level, acute exposures to CO can result in basal ganglia damage and parkinsonism, chronic exposures to CO in the home or workplace can result in pre-clinical changes that are similar to those seen with excessive exposures to Mn. Exposures to CO that cause symptoms are similar to those seen among some welders. Blood carboxyhemoglobin (COHg) levels have reached 20% in gas-shielded metal arc welders welding with poor ventilation and a CO₂ gas shield. CO levels may reach 100ppm with air-arc gouging of steel with a carbon and graphite electrode (Sjogren, 1994). The shielding gas in MAG welding may contain 20% CO₂ with CO exposures to 50 ppm or more occurred in 10% of cases with peak exposures of 150 ppm (Ulfvarson, 1981).

Johnson et al. (1974) evaluated 6 non-smoking toll booth attendants in central Kentucky. The major emission pollutant affecting short term performance was carbon monoxide. Performance tests were given before and after work. There were significant associations between increases in COHg and impaired time-shared performance and tapping. Acute CO exposures sufficient to yield a COHg level of 5% will degrade complex, demanding performance.

Dorello (1938) investigated illness among crew of a diesel-powered submarine. By 7 days after submersion 70% of crew were affected. Symptoms included vertigo, visual

disturbances, mask-like facies, and depression. Symptoms completely resolved by 7 months after the voyage. An investigation identified the presence of carbon monoxide.

Jensen et al. (1989) examined 11 garage workers who had been exposed to diesel exhaust fumes for 2-29 years. Acute symptoms included vertigo, headache, and fatigue. 6 of 7 with more than 5 years of exposure complained of memory problems, difficulty with concentration, irritability, sleepiness and reduced libido. Neuropsychological testing of 6 demonstrated slight changes of organic brain damage in 5.

Jovanovic et al. (1999) compared 250 professional drivers exposed to an average of 71.2 ± 8.1 ppm CO to a control group of 120 professional drivers exposed to an average of 5.4 ± 1.2 ppm CO. Exposed drivers had more frequent symptoms of headache, irritability and vertigo and a prolonged reaction time with visual or acoustical stimulation.

Myers et al. (1998) found that individuals with chronic CO poisoning (such as furnace exhaust leaks in homes) have extreme motor and cognitive slowing. In 6 tested cases, all had slow finger tapping performance, decrements in logical memory and abnormal trails tests (A and B). Exposures had ranged from 1-18 months.

Wright et al. (1973) treated 50 adults with 80 mL of CO. Carboxyhemoglobin levels increased from an average of 2.9 to 6.3% (4.4 to 7.0% for smokers and 1.3 to 5.6% for non-smokers). Reaction time was significantly depressed in exposed compared to controls 30-40 minutes after exposure.

Neurobehavioral changes in experimental animals with Mn exposures

Normandin et al. (2004) exposed rats for 30 hours per week for 13 weeks to $3000 \mu\text{g}/\text{m}^3$ Mn as Mn phosphate or Mn phosphate/sulfate or to $4000 \mu\text{g}/\text{m}^3$ as metallic Mn. Brain Mn levels were higher with exposure to Mn salts. In the striatum, Mn levels increased by 76% with metallic Mn exposure, 116% with Mn phosphate exposure and 147% with Mn phosphate/sulfate exposure. No neurobehavioral changes were seen with metallic Mn or Mn phosphate exposures but there was a decrease in ambulatory activity with Mn phosphate/sulfate exposure.

Ulrich et al. (1979a,b) exposed monkeys rats 24 hours a day for 9 months to 112.5 - $1152 \mu\text{g Mn}/\text{m}^3$ as Mn_3O_4 . They found no limb tremor or EMG abnormalities, findings seen in workers or experimental animals with excessive Mn exposures. There were no exposure-related clinical signs and no Mn-related microscopic changes of the brain.

Derivation of a threshold limit for manganese exposure

Roels et al. (1992) evaluated workers exposed to Mn at a dry alkaline battery plant. They measured cumulative Mn exposures and compared these to neuropsychological test results after dividing exposed workers into 6 exposure categories. Using logistic regression model and a benchmark approach at the 5% level, the NOEL for hand steadiness (95% upper bounds) was a cumulative exposure index (CEI) of $0.730 \text{ mg}\cdot\text{yr}/\text{m}^3$ (respirable Mn) and $3.575 \text{ mg}\cdot\text{yr}/\text{m}^3$ (total Mn). The authors assumed that exposure had remained constant for the working lifetime of each worker. With this assumption, the NOEL exposure for hand steadiness was an average of $0.138 \text{ mg}/\text{m}^3$ (respirable Mn) and a total Mn of 0.674

mg/m³. This compared with current geometric mean exposures of 0.215 mg/m³ respirable Mn and 0.948 mg/m³ total Mn. Overall, CEIs of above 1.200 mg-yr/m³ (respirable Mn) and 6.000 mg-yr/m³ (total Mn) were associated with slight neurophysiological changes in a significant proportion of the population. The authors found that hand steadiness was the most appropriate parameter to define a threshold effect.

Lucchini et al. (1995), in their evaluation of 58 ferromanganese alloy plant workers, found that the NOEL for pre-clinical neurophysiological effects appeared to be that reflected by the intermediate group with a geometric mean exposure of ranging from a high of 0.319 to a current value of 0.124 mg/m³. At the LOEL exposure level, the high geometric mean total Mn exposure was 1.590 mg/m³ with a current geometric mean exposure of 0.270 mg/m³. Average cumulative exposure indexes (in terms of respirable dust) were 0.177, 0.199 and 0.668 mg/m³ for average exposure times of 12.9, 11.8 and 13.8 years. Average exposures would then be: 0.0137, 0.0168 and 0.0484 mg/m³ with a NOEL of 0.0168 mg/m³ and an LOEL of 0.484 mg/m³.

USEPA's inhalation reference concentration (RfC) for manganese was set in 1993 at 0.05 µg/m³. Particular weight was placed on the study Roels et al. (1990, 1992) from which an exposure-adjusted LOEL of 0.050 mg/m³ derived from a minimum effect CEI of 0.793 mg/m³-yr and an average workplace exposure of 0.150 mg/m³. USEPA obtained individual data from Roels and re-analyzed the data against various endpoints, exposure-effect models and uncertainty factors. The most plausible estimates of the RfC were judged to fall in a range of 0.09 to 2 µg/m³. USEPA discounted the results of Mergler et al. (1993) because exposures were measured as area samples using stationary monitors instead of by a personal sampling technique (USEPA, 1997; Davis, 1998; Davis, 1999).

ATSDR (2000) set an inhalation minimum risk level ((MRL) for manganese at 0.040 µg/m³ based on Roels et al. (1992) study using a bench mark dose method with a 95% confidence limit for a 10% increase in risk. The authors provided sufficient data on individual participants to develop a dose-response relationship. The calculated NOEL was 74 µg/m³ as respirable manganese. A second benchmark dose analysis was performed on data from individual participants in the study of Iregren (1990). In this case the BMDL₁₀ NOEL level was found to be 71 µg/m³ with a conversion to respirable manganese based upon the reported observation that the respirable fraction ranged up to 0.80 of total dust. The MRL was then developed by converting the workplace NOEL to a continuous exposure level and impose an uncertainty factor of 500. ATSDR discounted the study of Mergler et al. (1994) which found neurobehavioral effects with exposures to a geometric mean of 40 µg/m³ as respirable Mn since exposures had decreased during the preceding 10 years from much higher values.

Health Canada's risk assessment for MMT (Egyed et al., 1996) was based on the study of Roels et al. (1992) as well as unpublished data supplied by Roels concerning frequency of abnormalities. When exposed workers were divided into quartiles based on cumulative exposures (mg-yr/m³), those in the lowest quartile had effects (visual reaction time, eye-hand coordination, hand steadiness) that were no different from controls. The cumulative exposure for this quartile averaged 0.264 mg Mn-year/m³ with an average of 2.6 years of exposure for 5 days/week, 8 hours/day. The average daily exposure was 0.101 mg/m³, an

NOEL level. Health Canada derived a continuous NOEL exposure level of 0.0315 mg/m³.

WHO (2000) used a benchmark approach and the Roels et al., 1990, data set for their risk assessment. The NOEL at a 10% effect level (95% lower confidence limits) was 74 µg/m³ respirable Mn and at a 5% effect level was 30 µg/m³. The latter was chosen by WHO as a conservative NOEL. WHO calculated a LOEL for continuous exposure to respirable Mn of 50 µg/m³ based on Roels et al. (1990). WHO also considered the LOEL of Iregren (1990) of 140 µg/m³ (total Mn) as an alternate LOEL to that of Roels et al.

A TLV-TWA of 0.2 mg Mn/m³, as Mn, was recommended by ACGIH for occupational exposure to elemental manganese and its inorganic compounds. This value was intended to minimize the potential for pre-clinical adverse effects in the lungs and central nervous system and adverse effects on the fertility of male workers exposed to manganese (ACGIH, 2001).

VI. Manganese- reversibility

Reversibility of findings in manganism

If exposure to Mn is curtailed shortly after symptoms of manganism appear, findings can resolve except for some disorders in gait and speech (Flinn et al., 1941). Conversely, continued exposures can result in irreversible changes.

Couper (1837) described 2 cases of manganism in workers who developed paralysis after working with manganese oxide. Both workers stopped exposure: one remained stable when re-evaluated 1 year later. In the second, symptoms of difficulty with speech and walking and excessive salivation were seen at the height of exposure. When removed from exposure there was no further progression of his illness and he was in good health when evaluated 6 years later.

Flinn et al. (1940) describe 6 cases of workers with manganism who had left work secondary to manganism. 4 improved, 1 had no improvement and 1 got worse after stopping work.

Arjona et al. (1997) describe a 54 year old construction worker who was in frequent contact with welders. He developed unprovoked falls, confusion, cogwheeling rigidity and a postural tremor of both arms. An MRI showed hyperintense signals on T1-weighted images in the right lenticular and caudate nuclei. Urine Mn was elevated at 24 µg/L. After 10 months without further exposure, mental confusion had disappeared, the MRI showed almost complete resolution of the high intensity signals and the urine Mn level was normal. The neurological exam was normal.

Bleich et al. (1999) describe a 14 year follow-up of an individual who developed manganism at age 66 from exposure to potassium permanganate. Most symptoms (muscle pain and cramps, fatigue, concentration problems, anxiety) improved. On examination there was continued impairment in coordination, slight dysarthria, shortening of the gait, a slight resting tremor and constant fasciculations. Overall there was no progression of the

illness as seen with PD. The blood Mn reduced from 15.0 to 0.48 $\mu\text{g}/\text{dL}$ but the hair Mn was higher at 2.79 ppm.

Kim et al. (1998) describe a worker who developed symptoms of difficulty walking and slurred speech at age 39, 10 months after being employed in a factory that produced raw materials for the manufacture of welding consumables. He retired 2 months later. Starting 2 months after retirement he progressively became worse with tremor with frequent falling in backward gait. When examined at age 52, he had facial masking, a resting tremor more marked on the right, bradykinesia, monotonous speech and impaired rapid alternating movements of both hands. There was dystonia of one foot. There was a slight, unsustained response to L-dopa. An MRI was normal and a fluorodopa PET scan showed normal uptake in the striatum.

Yamada et al. (1986) describe a worker who, 12 years after beginning working at a Mn ore crushing plant, developed euphoria, emotional lability, facial masking, monotonous speech, increased muscle tone, tremor of the eye lids, difficulty in walking backwards. Urine Mn was 104 $\mu\text{g}/\text{L}$ and blood Mn was 3.4 $\mu\text{g}/\text{dL}$. EDTA treatment increased urine Mn to 564 $\mu\text{g}/\text{L}$. There was no clinical improvement with this treatment or to L-DOPA. He died of cancer 15 years after last being exposed. At autopsy there was atrophy and loss of cells of the pallidum, putamen and caudate nucleus with the remaining cells shrunken. There was marked decrease in myelinated fibers, increase in astrocytes and proliferating glial fibers in the pallidum. The nerve cells in the thalamus and cerebral cortex were shrunken. Brain Mn levels were similar to those of controls.

Huang et al. (1993) identified 6 patients with Mn intoxication at a ferromanganese smelter. All were removed from exposure within 5 months of diagnosis. They were re-evaluated on a monthly basis at a neurological clinic. Gait disturbances became progressively worse over next 4 years, particularly with turning and walking backwards. L-dopa treatment was used in 3 with improvement for 2-3 years then a decrease in response. Age at diagnosis ranged from 36-48. On neurological exam, abnormalities were found with 5/5 with micrographia, 3 with mask like facies, and 3 with hypophonia, 4 with dystonia and 5 with difficulty walking backwards. None had a tremor. The authors further evaluated 5 of these workers 10 years after exposure ceased (Huang et al., 1998). Findings had worsened, particularly gait, speech, writing, rigidity, speed of foot tapping. In previous studies of these same patients, PET scanning showed no significant fluorodopa uptake but there was widespread decline in cortical glucose metabolism when tested against ^{18}F -2-fluoro-2-deoxyglucose. There was minimal reduction in C-raclopride D_2 receptor binding in the caudate but normal reduction in the putamen on PET scanning suggesting no major changes in striatal D_2 receptors. These data suggest that presynaptic and even the receptor level postsynaptic striatal dopaminergic functions appear to be unimpaired. The authors conclude that these studies suggest that in manganese long-term progression can occur but not from damage to the dopaminergic projection.

Reversibility of findings of pre-clinical manganese intoxication

Improvement (or non-progression) is likely when exposures are either curtailed or controlled when there are only pre-clinical findings. Roels et al. (1999) evaluated workers in 1987 at a dry alkaline battery plant where there was an average total Mn exposure of 1 mg/m^3 . Workers had been exposed for an average of 5.5 years. Workers were studied for

an additional 8 years to see whether neuropsychological abnormalities improved as exposure decreased. A local exhaust system was in place since the installation of assembly lines in 1968. Technological improvements were made in the powder room (where 15 workers were employed) in 1977. All workers who had been employed in the powder room prior to 1977 had left by 1987. No historical data on exposure was available prior to the 1987 study. In 1987 changes were made to decrease Mn exposures at different job sites in the plant. The authors evaluated 161 workers longitudinally. By 1995, 34 were still in exposure areas. They also evaluated 24 workers who left Mn exposure areas between 1988 and 1992 as well as a group of 32 controls from the 1987 study. The geometric mean total Mn exposure level was $795 \mu\text{g}/\text{m}^3$ in 1987. Starting in 1992, levels dropped reaching $250 \mu\text{g}/\text{m}^3$ in 1994-5. In the lowest exposed group, total Mn prior to 1992 was about $400 \mu\text{g}/\text{m}^3$. In the high exposure group, geometric mean total Mn exposures were $744 \mu\text{g}/\text{m}^3$ in 1994. In that year exposures in the low and moderately exposed groups were 119 and $181 \mu\text{g}/\text{m}^3$ respectively. Eye-hand coordination improved in each group reaching control values in the lowest exposed group by 1992. The medium exposure group values were still 12% less than controls. Among ex-Mn exposed workers, eye-hand coordination improved in workers in the 3 exposure groups with average values similar to controls in the lowest exposed group. There was no improvement in hand steadiness and simple visual reaction time during the follow-up interval.

Lander et al. (1999) evaluated 24 furnacemen at 3 small cast iron foundries where the iron contained 0.5-2% Mn. 2 of the foundries had poor ventilation and produced twice as much product each as the third, a foundry with adequate ventilation. Mn exposures at one foundry with poor ventilation averaged 39, range $7\text{-}64 \mu\text{g}/\text{m}^3$ while exposures at the well ventilated foundry averaged $5 \mu\text{g}/\text{m}^3$. Blood Mn levels of workers at the 2 poorly ventilated foundries averaged $1.40 \mu\text{g}/\text{dL}$ while that of workers at the well ventilated foundry averaged $0.92 \mu\text{g}/\text{dL}$. Control blood Mn levels averaged 0.87 and $0.88 \mu\text{g}/\text{dL}$. Blood Mn values were retaken from workers at the 2 poorly ventilated foundries 3-4 weeks after they stopping work. Blood Mn dropped to an average of $1.06 \mu\text{g}/\text{dL}$ (range $0.81\text{-}2.9 \mu\text{g}/\text{dL}$). A screening medical history of all workers identified 2 workers with slight central nervous system symptoms of decreasing memory, fatigue, irritability and sleep disturbances. Their blood Mn levels were 2.5 and $2.9 \mu\text{g}/\text{L}$. After 6 months with reduced or no exposure, blood Mn values were 1.41 and $0.94 \mu\text{g}/\text{dL}$ and their symptoms had cleared.

Crump & Rousseau (1999) evaluated workers at same factory as evaluated by Roels et al. in 1983 (see Roels et al., 1987a,b) using the same protocol and equipment but extended evaluation for an additional 11 years. 114 of the 141 Mn-exposed workers evaluated by Roels et al. were included. 44 of these workers were evaluated at least twice 8 years or more apart. Average yearly Blood Mn levels were similar over the 11 years to levels found by Roels et al. with means ranging from 1.1 to $1.5 \mu\text{g}/\text{dL}$ (compared to 1.36 found by Roels et al.). Average yearly urine Mn values ranged from 3.2 to $30 \mu\text{g}/\text{g}$ creatinine (compared to $4.76 \mu\text{g}/\text{g}$ creatinine for Roels et al.). For all workers, mean reaction times improved compared the Roels study. The instrument used for measuring eye-hand coordination was the same as in the Roels et al. study through 1990 at which time it was changed. During this interval mean percent precision improved in studied workers. Hand steadiness correlated with blood Mn levels while memory and eye-hand coordination

correlated with age. There was no relationship between measures of urine Mn and any neurological test outcome. The average duration of Mn exposure increased from 7 years in 1985 to 14 years in 1996. Memory (in terms of errors and repetitions) improved during the study while there were no decrements in reaction time. Eye-hand coordination improved until 1990. After the change in test instruments, there was no further change. Hand steadiness varied from year to year and correlated with blood Mn levels. When limiting the analysis to the 44 workers who were followed for at least 8 years, similar findings were seen for hand steadiness and there was significant improvement in reaction times, the 2 parameters evaluated. Age but no Mn variable was related to changes in memory or eye-hand coordination. Roels et al. also found a dose-response relationship between hand steadiness and blood Mn but not reaction time or short-term memory. They also found a relationship between blood Mn and eye-hand coordination, a relationship that was not maintained in this study. Roels et al. found a relationship between hand steadiness on hole 4 of their instrument and blood Mn. The authors conclude that the additional 11 years of testing do not suggest any progression of clinically detectable signs even with continued Mn exposure. On a gross basis there did not appear to be any trend toward poorer performance on neurological tests despite the fact that the exposed population was aging.

Kafritsa et al. (1998) evaluated 2 children receiving parenteral nutrition whose Mn supplementation was stopped before a movement disorder developed. Whole blood Mn decreased to a normal range without treatment and MRIs, which had shown T1-weighted signal hyperintensity of the basal ganglia, reverted to normal. The authors conclude that when movement disorders have not occurred, Mn leaves the brain and the prognosis is good.

Hochberg et al. (1996) examined Chilean miners who had had high level exposures to Mn dust exposure for an average of 20.3 years but no exposures for at least 5 years. Standardized tests were made of tremor, repetitive hand movements and tapping and compared to a control group of miners with low or no exposures to Mn. Miners were asymptomatic with no evidence of manganism. Neurological examinations showed increased resting and action tremors and movements that were slower and less facile than those seen in controls. Neurophysiological testing showed increased frequency of resting and action tremors and decreased hand speed and steadiness. Tapping was normal.

Lucchini et al. (1999) conducted a follow-up study of workers at a ferroalloy plant. A previous study of same workers in 1995 had showed abnormalities (addition, digit-span, finger tapping, symbol digit) in high level exposed workers. Significant improvement in Mn exposure levels had occurred associated with improved ventilation in 1988-9. Average exposure of mid group was 0.097 mg/m^3 . There were no cases of possible or probable PD based on a parkinsonism questionnaire. There were no differences in reaction times and tests of coordination (hand pronation-supination) compared to controls. There was higher tremor frequency in exposed workers but amplitude and harmonics were no different between exposed and controls. Digit-span and addition were more affected in Mn workers. A comparison of results of SPES tests (symbol digit, finger tapping, and digit span) in 30 workers tested in 1990-1 and again in the present study did not show any differences. There was a correlation between digit span, finger tapping and symbol digit

and cumulative exposure index. There were no differences in average visual contrast sensitivity at different frequencies between exposed and control workers. There was increased frequency of symptoms of irritability, equilibrium loss and rigidity among exposed workers. The authors could not exclude a contribution of high earlier exposures to the findings in exposed workers.

Reversibility of Mn findings in experimental animals

Oner and Senturk (1995) dosed female rats orally with 357 µg of Mn (as MnCl₂) daily for 15 days. At the end of 15 days, average hippocampal Mn was 0.82 ppm compared to 0.48 ppm in untreated controls. The rats performance time on a previously learned T maze declined to 104.5 seconds compared to 28.7 seconds in untreated controls. After 15 days without further exposure, hippocampal Mn had decreased to 0.64 ppm with a corresponding improvement in T maze time (55.7 sec). The authors note that the T maze is thought to be a measure of hippocampal function.

Treatment of manganese intoxication

Findings of manganese intoxication reverse with treatment with some chelating drugs including CaNa₂EDTA and PAS sodium. DMSA, an effective chelator for lead poisoning, is ineffective for mobilizing Mn. Treatment is sometimes effective even when instituted years after the onset of symptoms. EDTA treatment can be repeated safely on a monthly schedule, even with renal failure (PDR, 2004). Although L-dopa is not useful in most cases, there are some reports where treatment is effective.

Angle (1995) compared treatment regimes in a ferromanganese alloy welder with manganism. He was treated with DMSA for 3 weeks without changes in his blood Mn levels or urine Mn excretion. EDTA treatment was effective in increasing urinary Mn excretion.

Hine & Pasi (1975) treated a 27 year old man who developed manganism after cutting and burning ferromanganese alloy for 4 years without personal protection or local exhaust ventilation. Mn levels at work were 11.5 mg/m³ where he spent most of his time. He was treated with EDTA daily for 6 days with a moderate clinical improvement over the next month. He had slow improvement for 12 months then dramatic improvement starting 18 months after exposure. At 24 months after exposure he had a nearly complete recovery.

Discalzi et al. (2000) describe a case of manganism in a welder treated with 3 EDTA treatment courses. Treatment (and removal from exposure) resulted in marked decreases in tremor, improvement in walking. Improvements allowed reduction in L-dopa dose from 300 mg to 185 mg/day. Blood Mn levels in 1998 were 1.44 µg/dl, decreasing to 0.45-0.85 µg/dL with EDTA treatment. By 1999 the gait was normal and the tremor had almost disappeared.

Smyth et al. (1973) found 5 workers with manganism on surveying employees at a ferromanganese alloy plant. All 5 were hospitalized and treated with 2 gm CaNa₂EDTA daily for 3 days. Treatment was associated with increased Mn excretion. They returned to work in Mn-free areas. 3 workers received a second course of treatment but this was not

associated with increased Mn excretion. Findings in the 2 workers with lack of associative arm movements resolved. Findings in the other 3 cases did not improve or deteriorate.

Cook et al. (1974) treated 2 cases of manganism with EDTA. In one case there was no improvement with treatment with 8 gm of L-dopa/day for 6 months. He was then treated with EDTA for 3 days with an increase in urine Mn from 7-10 µg/L to 15-32 µg/L. Treatment was associated with a dramatic improvement in walking and getting out of a chair. Repeated treatment 6 months later resulted in substantial improvement in facial masking, retropulsion, postural stability and bradykinesia. Improvement was not maintained. In a second case, EDTA treatment resulted in improved gait, coordination, ability to walk backwards, signature, rapid alternating movements and facial masking. The improvement persisted for at least 4 months.

Whitlock et al. (1966) describe 2 employees at a ferromanganese alloy plant developed manganism after a process change that required trimming of castings with an air arc burner. In the first case a 54 year old developed forgetfulness, incoordination, unsteady gait, facial masking monotonous voice, increased plastic rigidity of all 4 extremities, symmetrical hyperactive reflexes, wide-based gait with unstable tandem gait, poor rapid alternating movements and a positive Babinski reflex. Urine Mn was 4.58 µg/L increasing to 150 µg/L after EDTA. Over the next 2-3 months he had improvement in his strength and coordination sufficient to allow him to return to work. Improvement persisted at 6 months post treatment. The second worker developed poor memory, facial masking, decreased associated movements with walking, instability when standing on one leg, slowed alternating and coordinated movements, hyperreactive reflexes and a positive Babinski reflex. There was slight plastic rigidity in all 4 extremities. A urine Mn was 5.48 µg/L increasing to 1000 µg/L with EDTA. There was immediate improvement associated with EDTA treatment with disappearance of Babinski reflexes and disappearance of rigidity, facial masking and incoordination. The improvement persisted when re-examined 6 months later. He was able to return to work. Cutting work was done in a 4-sided booth without local exhaust ventilation. Total Mn levels during cutting ranged from 2.3-4.7 mg/m³.

Tanaka and Lieben (1969) treated a manganese burner with manganism with CaNa₂ EDTA in 2 courses 2 months apart. There were significant elevations of Mn excretion each time. There was marked improvement in his symptoms and some improvement in his neurological exam after the 2nd treatment.

Flinn et al. (1941) treated 6 patients with manganism with EDTA. Two had no improvement. Four, however, had positive responses to short courses of EDTA. There was no response to a placebo infusion. Two of the four had persistent improvement. Long term treatment was not used because of the potential for nephrotoxicity with EDTA.

Nagatomo et al. (1999) reported on 2 cases of manganism where an Mn supplement had been added to the total parenteral nutrition (TPN) solution such that they received 1100 µg of Mn per day. In the first case marked confusion, rigidity, facial masking and vertical gaze palsy developed in a 68 year old woman 3 months after starting TPN. Her serum Mn was 4.2 µg/dL. An MRI showed hyperintense T1-weighted signals of the basal ganglia,

particularly the globus pallidus. She was treated with EDTA for 5 days with urine Mn increasing from 10-20 µg/L to 150-180 µg/L. The abnormal MRI resolved in 3 months. In the 2nd case, a 70 year old man developed signs of manganism after 4 months of TPN with a Mn-supplemented solution. He developed a gait disturbance, confusion, marked rigidity, facial masking and a resting tremor. An MRI showed hyperintense T1-weighted signals of the basal ganglia, particularly the globus pallidus. His serum Mn was 5.1 µg/dL. Treatment with EDTA resulted in an increase of his urine Mn from <10 µg/L to 210 µg/L. There was gradual improvement in his parkinsonism after the EDTA treatment and discontinuation of the supplement.

Ono et al. (2002) describe a 17 year old welder who developed myoclonic involuntary movements after welding for 2 years in a plant that used Mn. He was treated with 2 gm calcium EDTA daily for 5 days associated with an increase in urine Mn from <1 to 30-31 µg/L. By the end of treatment there was marked improvement in his involuntary myoclonic movements. Immediately after treatment, T1-weighted high intensity signals had become less evident and resolved by 3 months after treatment. His blood Mn was 4.3 µg/L (normal 0.8-2.5) decreasing to 2.5 µg/dL immediately after treatment. At a follow-up 3 months later, his blood Mn was 1.6 µg/dL

A 3 year old child was treated for acute Mn intoxication associated with status epilepticus with CaNa₂EDTA. Seizures were not responsive to epileptic drugs. Treatment promptly reverses acute brain toxic effects of Mn with normalization of the EEG. Blood Mn levels returned to normal (Herrero et al., 2003).

Ibim et al. (1992) treated dogs with a single dose of CaNa₂EDTA Treatment resulted in the increased urinary excretion and decrease in hair levels of Mn. The authors concluded that this treatment was effective in mobilizing Mn from storage sites and reducing body burden.

After treatment with L-dopa for 6 months was ineffective, Cook et al. (1974) treated one of their cases of manganism with EDTA for 3 days with an increase in urine Mn from 7-10 µg/L to 15-32 µg/L. Treatment was associated with a dramatic improvement in walking and getting out of a chair. Repeated treatment 6 months later resulted in substantial improvement in facial masking, retropulsion, postural stability and bradykinesia. Improvement was not maintained. In a second case, EDTA treatment resulted in improved gait, coordination, ability to walk backwards, signature, rapid alternating movements and facial masking. The improvement persisted for at least 4 months.

Wynter (1962) treated 7 cases of manganism that originated in a mine before the ventilation/drilling changes with EDTA 4 years or more after last exposure. All received some benefit from the treatment. One case first developed symptoms 6 years after exposures to Mn decreased. Prior to that he had been dry drilling Mn ore for 2 years. He developed a gait disorder and was immediately treated with EDTA while he continued to work at the mine. Neurological findings resolved and did not return during 4 years of follow-up.

Penalver (1957) described a case of manganism in a 47 year old underground rock driller at an unventilated MnO₂ mine. He worked for 18 months at age 32 and again starting age 33 for 2 and ½ years. He began having impulsive acts and absent-mindedness. During the next months he developed leg weakness, impotence, aphonia, facial masking, torticollis, hyperreflexia, inability to walk and tremors. He was treated with EDTA. Improvement began within the month and by 11 months later he was able to work as a gardener with almost complete recovery.

Ky et al. (1992) describe 2 cases of manganism. The first was a 50 year old woman who was exposed to MnO₂ for 21 years, ending at age 45. She had had a tremor starting at age 27. At age 43 she had the onset of rigidity and on exam had tremor of her tongue and hands, hypertonicity, and a dragging gait and she was treated with 2 courses of CaNa₂EDTA with improvement but exposures continued and symptoms returned. Symptoms worsened with L-dopa. At age 47 she was again treated with 2 courses of EDTA with improvement. When symptoms returned 6 months later she was treated with para-aminosalicylic acid (PAS-Na), a drug used to treat tuberculosis, 6 gm in 500 mL of 10% glucose 4 days a week for 3 ½ months. Hypersensitivity reactions can occur with this class of drugs but other side effects are infrequent (PDR, 2004). All symptoms, including facial masking, speech problems, tremor, cogwheeling rigidity, micrographia, and her gait disorder resolved and her grip strength increased by 5 kg. When followed up 19 months later, symptoms and signs were normal. During PAS-Na treatment her urine Mn excretion increased from 3.11 to 6.79 µg/24 hours. A second worker had been exposed to MnO₂ while crushing ore for 4 years ending at age 36. Mn exposures in his workplace ranged from 25-83.3 mg/m³. He first developed symptoms at age 35 with purposeless weeping and laughing, tiredness, difficulty walking up hill and muscle tics with tremor, difficulty speaking, hypertonia, and a hurried gait on examination. By age 53 he was unable to walk without a crutch. Beginning at age 61 he was treated with PAS-Na for 3 ½ months. With treatment he had improvement in his facial masking, speech difficulties gait, hand writing and clearing of his tremor and cogwheel rigidity. Improvements persisted at the time of a 6 month follow-up. During treatment his urine manganese excretion was 7.76 µg/24 hours decreasing to 3.1 µg/24 hours after treatment. The authors note that 3-4 courses of treatment with EDTA will result in improvement in 60% of mild Mn poisoning cases but will not result in improvement of a full-blown parkinsonian syndrome.

Rosenstock et al. (1971) treated a worker with manganism who first developed symptoms 14 years before treatment. He was treated with a single dose of 1 gm of EDTA and his urine Mn over the next 3 days ranged from 35-52 µg/L followed by treatment with L-dopa 12 g/day. Treatment was associated with the return of his muscle tone to normal, loss of snout, glabellar and Babinski reflexes, loss of his action tremor and improvement in his bradykinesia, dysarthria, dysdiadochokinesia and facial masking. His accuracy on objective testing of fine motor performance improved.

Huang et al. (1989) treated 6 workers who developed manganism while working in a ferromanganese alloy plant. All responded well to treatment with L-dopa/carbidopa for 8 weeks. Blood Mn values ranged from 10.2-40.5 µg/dL (normal 0.7-1.2), scalp Mn ranges from 27.7-445.2 ppm (normal 0.1-2.2) and pubic hair Mn ranged from 26.7-2735.5 ppm

(normal 0.3-9.8 ppm). There was no response with treatment with CaNa_2EDTA in 3 of the patients over 8 weeks.

EDTA treatment of Mn-intoxicated experimental animals

Kosai and Boyle (1956) treated Mn-poisoned rats with subcutaneous injections of EDTA 3 times a week for 3 weeks. Treatment resulted in the marked increase in Mn excretion in the urine. Liver Mn levels were 38% of Mn intoxicated rats not receiving treatment.

VII. Medical monitoring

Although routine industrial hygiene monitoring can be protective of workers, most exposures to manganese occur in situations where there are infrequent measurements of exposure. Exposures to potentially toxic chemicals can also be assessed by measuring the chemical in a body fluid or by looking for early physiological effects of that chemical.

Biological monitoring: Blood/urine

Although the biological half-life for blood Mn is <5 minutes, blood Mn can be increased in Mn workers, even after exposure ceases. When one finds increased blood Mn levels after chronic exposure it is likely secondary to increased body stores (primarily in the lungs) with slow release from these stores (Smargiassi & Mutti, 1999). Control urine Mn levels average 0.09-0.30 $\mu\text{g}/\text{gm}$ creatinine or 1-8 $\mu\text{g}/\text{L}$, control blood Mn levels average 0.57-1.16 $\mu\text{g}/\text{dL}$, and serum Mn average 0.25 $\mu\text{g}/\text{L}$ (Roels et al., 1985, 1987b, 1992; Tsalev et al., 1977; Arjona et al., 1997; Papavasiliou & Cotzias, 1961). Relationships between average Mn exposures and average urine and blood Mn levels are summarized in the table below.

A number of studies have looked at the usefulness of measures of manganese in the body (blood manganese) or the urinary excretion of manganese as surrogates of industrial hygiene measurements of exposure. Lucchini et al. (1995) evaluated 58 ferromanganese alloy plant workers 1-42 days after their last exposure. During the preceding 10 years, total Mn levels had decreased from a geometric means of 0.070-1.59 mg/m^3 to geometric means of 0.027-0.270 mg/m^3 . Average respirable Mn exposures per year, based on area samples, were 13.7, 16.8 and 48.4 $\mu\text{g}/\text{m}^3$ in the low, medium and high exposure groups. The geometric mean blood Mn was 0.6 $\mu\text{g}/\text{dL}$ for the low exposure group, 0.86 $\mu\text{g}/\text{dL}$ for the medium and 1.19 for the high exposure group. There was a good correlation between log blood Mn and log cumulative exposure index (CEI) with an r of 0.60 ($p < 0.01$). There was also a dose-effect relationship between blood Mn and neurobehavioral test outcomes but no relationship between CEI and test outcomes after correcting for the vocabulary test score. This study found a correlation between CEI and blood Mn not found on previous studies. The authors hypothesized that this may be explained by a period without exposure before blood Mn levels were drawn: blood levels would be more likely to reflect body stores and not recent exposure. Urine Mn ranged from geometric mean values of 1.2-2.8 $\mu\text{g}/\text{L}$. There was also a significant correlation between CEI and urine Mn.

Roels et al. (1987a) evaluated 141 workers exposed to Mn oxides and salts for an average of 7.1 years. Overall mean and median exposures to Mn were 1.33 and 0.97 mg/m^3 .

Production began in 1964 with no environmentally significant changes to the plant since that time. However, production of MnO₂ increased systematically from 2800 mt in 1970 to 22000 mt in 1981 without concomitant improvements in ventilation. A single, blind neurological examination was conducted to detect early signs of parkinsonism, including rigidity, cog-wheeling, balance, tremor, and mask-like facies. There were more smokers among the Mn-exposed population. Except for trunk rigidity, no significant differences were identified on these examinations between exposed and control groups. Urine Mn dropped rapidly when exposure ceased with a half-life of 30 hours. There was no relationship between blood and urine Mn and no correlation between blood Mn and current exposure levels. When splitting workers into 6 exposure groups, the average blood Mn for these groups correlated with estimates of cumulative exposure, eye-hand coordination and hand steadiness, but not simple reaction time or short-term memory.

Tsalev et al. (1977) found that mean blood Mn values ranged from 1.1-1.6 µg/dL (controls 1.0 µg/dL) among Norwegian ferromanganese alloy workers exposed to an average of 1 mg Mn/m³ over the last 5 years. 11 workplaces were identified in a plant producing Mn oxides and salts. Mean exposure levels for these workplaces for total Mn correlated with mean urine Mn (UMn) with an $r = 0.62$ ($p < 0.05$).

Roels et al. (1992) evaluated 92 Mn-exposed workers at a dry alkaline battery plant with a total work force of 1100 workers of whom 102 were currently exposed to Mn. The authors found no correlation between blood Mn or urine Mn and various exposure parameters. When they divided the workplace into 6 exposure categories, there was an excellent correlation between mean air values and geometric mean urine values ($r = 0.83$, $p < 0.05$). Since urine Mn, when analyzed on a group basis, correlated with current exposure levels, the authors felt that this parameter may be useful as a biological index for current exposure.

Luccini et al. (1999) did a follow-up of study of 61 ferromanganese alloy male workers and 87 controls seen at the same plant as in their 1995 study. The geometric mean total manganese concentrations at the plant have changed from 1981 to 1997 from 1.60 mg/m³ to 0.239 mg/m³ in the furnace area; from 0.151 to 0.256 mg/m³ in the casting area; and from 0.167 to 0.055 mg/m³ in the maintenance areas where welding operations were conducted. The cumulative exposure index (CEI) during this period had a geometric mean value of 1.205 mg Mn/m³-yr with an overall average exposure of 0.071 mg Mn/m³. Geometric average blood and urine Mn were significantly higher in the exposed workers (9.18 µg/L and 1.53 µg/g creatinine, respectively) than in controls. A positive correlation was observed between Mn air levels and blood Mn ($r = 0.36$, $p = 0.0068$). There was no association between CEI and either blood or urine Mn.

Lucchini et al. (1997) evaluated furnace and casting workers at a ferromanganese alloy product plant who were exposed to manganese oxides. Total Mn levels ranged from 0.026-0.750 mg/m³ with an average of 0.093 mg/m³ and a geometric mean of 0.193 mg/m³. There was an excellent relationship between log blood Mn and log cumulative exposure index ($r = 0.52$, $p < 0.002$). Hand-eye coordination (aiming pursuit) deteriorated with increasing blood Mn levels with an $r = 0.36$, $p < 0.05$. Blood Mn among exposed workers had a geometric mean of 0.98 µg/dL vs. 0.68 µg/dL in the control group. Urine

Mn levels had a geometric mean of 3.0 µg/L in exposed workers vs. 0.43 µg/L in the control population.

Wang et al. (1989) evaluated 132 workers at a ferromanganese smelting plant where a case of manganism had occurred. Exposure in the highest exposure area averaged 28.8 mg/m³. Other exposures ranged from 0.1-1.5 mg/m³. Blood Mn levels increased with increasing exposure from an average of 1.49 µg/dL in controls and to an average of 14.6 µg/dL in the high exposed group. Individuals exposed to 0.5-1.5 mg Mn/m³ had an average blood Mn level of 3.13 µg/dL and those exposed to 0.1 mg Mn/m³ had average blood Mn level of 2.52 µg/dL.

Crump & Rousseau (1999) evaluated workers at the same factory as studied by Roels et al. in 1983 (see Roels et al., 1987a,b) using the same protocol and equipment but extended the evaluation for an additional 11 years. 114 of the 140 Mn-exposed workers evaluated by Roels et al. were included. 44 of these workers were evaluated at least twice 8 or more years apart. Average yearly blood Mn levels were similar over the 11 years to levels found by Roels et al. with means ranging from 1.1 to 1.5 µg/dL (compared to an average of 1.36 µg/dL found by Roels et al.). Average yearly urine Mn values ranged from 3.2 to 30 µg/g creatinine (compared to 4.76 µg/g creatinine found by Roels et al.). Hand steadiness correlated with blood Mn levels. There was no relationship between measures of urine Mn and any neurological test outcome.

Deschamps et al. (2001) evaluated 114 workers at an enamel production company who were exposed to MnO₂ at an average respirable Mn concentration of 0.057 mg/m³. Regression analysis showed no significant relationship between length of employment and blood Mn.

Although blood and/or urine Mn may be useful for evaluating population-exposure relationships, average values for blood and urine Mn are similar to those of control populations at low level exposures (0.1-0.4 mg/m³) (Lucchini et al., 1997; Teresa et al., 1997). A study by Luccini et al. (1995) gives the only evidence that suggests that blood and urine Mn levels correlate with Mn exposures on an individual basis. This study differs from others in that there was a hiatus of 1-44 days between when a worker was last exposed and when urine and blood Mn levels were measured (ATSDR, 2000). ACGIH has not adopted a biological exposure determinant for Mn (ACGIH, 2005).

Table 3: Exposure to Mn and its relationship to blood and urine Mn levels

Study	Exposure (mg/m ³)	Blood Mn (µg/dL)	Urine Mn µg/L	Urine Mn µg/gm creat.	Reference
Smelter	28.8 av.	14.6* av.			Wang et al., 1989
Smelter	0.5-1.5	3.13 av.			Wang et al., 1989
Smelter	0.1 av.	2.52 av.			Wang et al., 1989
Battery plant	3-18	1.7-2.3*			Emara et al., 1971
Fabrication welders	0.31 av.	1.3-5.2	3-87		Chandra et al., 1981
Fabrication welders	0.57 av.	1.3-4.4	5-240		Chandra et al., 1981
Ship repair shop welders	1.74 av.	1.0-2.6	3-45		Chandra et al., 1981
MS welders	0.36 av.	1.65 av.	0.31 av.		Jarvisalo et al., 1992
Fabrication welders	1.45 av.	0.29 av.			Li et al., 2004
Fabrication welders	0.11 av.	0.066 av.			Li et al., 2004
Ferromanganese alloy factory	>2	6.72 av.	132 av.		Hua and Huang, 1991
MnO ₂ /Mn salt production	0.97 median	1.36 av.		4.76 av.	Roels et al., 1985, 1987a,b
Battery plant	0.215 resp g.m.	0.81 g.m.		0.84 av.	Roels et al., 1992
Ferromanganese alloy factory	0.0484 resp av.	1.19 g.m.	2.8 g.m.		Lucchini et al., 1995
Ferromanganese alloy factory	0.0.0168 resp av.	0.86 g.m.			Lucchini et al., 1995
Ferromanganese alloy factory	0.0137 resp. av.	0.6 g.m.	1.2 g.m.		Lucchini et al., 1995
Furnace & casting workers	0.193 g.m.	0.98 g.m.	3.0 g.m.		Lucchini et al., 1997
Ferromanganese alloy factory	0.65 av.			17.8 av.	Siqueira & Moraes, 1989
Ferromanganese alloy factory	0.28 av.			10.3 av.	Siqueira & Moraes, 1989
Welding school	0.43 av.	0.82		0.67	Teresa et al., 1997

*cases of manganism identified

av. = average; g.m. = geometric mean; resp. = respirable Mn exposure

Magnetic resonance imaging

Manganese is a paramagnetic element and excessive brain levels can be picked up with magnetic resonance imaging (MRI) studies. Abnormalities in MRIs can be seen with manganese exposures with or without clinical findings of manganism. Abnormalities resolve in 6 mos to 2 years once exposures cease and faster when there is treatment with EDTA. Although MRIs can show excessive body burden of Mn at a pre-clinical level, these studies must be done in a hospital setting taking more than an hour to perform. MRIs would not appear to be appropriate screening tools for detecting early excessive Mn exposures to workers exposed to Mn.

Kim et al. (1999b) evaluated workers exposed to Mn during welding (34), smelting (39) and welding electrode manufacturing (16). There were 35 controls. Exposures averaged 0.53 (range 0.1-1.56) mg/m³ for welders, 0.14 (range 0.08-1.4) mg/m³ for smelters, and 0.15 (range 0.02-0.42) mg/m³ for welding rod manufacturers. There were enhanced signals in 73.5% of welders, 41% of smelter workers and in none of welding rod manufacturing workers or controls. No signs of rigidity, bradykinesia, or walking problems were observed during 6 months of follow-up and neurological examinations showed no signs of manganism. Some postural tremor was seen but the incidence was no different between groups.

Kafritsa et al. (1998b) describe 2 children who were given parenteral nutrition that included a Mn salt resulting in high blood levels and T1-weighted high signals on MRI studies of the basal ganglia. In the first case, parenteral nutrition containing Mn had continued for 63 months. Blood Mn levels initially were 1.78 µg/dL in one case (reference range 0.40-1.16 µg/dL), dropping to 1.24 µg/dL 3 years after discontinuing parenteral Mn. Abnormal MRI signals did not decrease until 2 years after stopping the Mn supplement. In the other case, parenteral nutrition had continued for 23 months. At that time, blood Mn was 2.78 µg/dL dropping to 1.15 µg/dL 3 years after discontinuing parenteral Mn. During the 3 years of follow-up, no neurological abnormalities were noted in either child and development was normal. Liver function was normal in each child.

Hauser et al. (1996) evaluated 11 patients with chronic liver failure. The patients have higher blood Mn levels (mean of 2.1 µg/dL) than controls. Semi-quantitative scores of T1 weighted signal hyperintensity on MRIs correlated with blood Mn levels with an r of 0.65 (p<0.05). Signal hyperintensity was found primarily in the globus pallidus, substantia nigra and putamen (6-10/11 cases) and to a lesser extent in the tectum and pituitary (2-3/11 cases).

Neurophysiological studies

Iregren (1994) reviewed all neurophysiological studies of Mn-exposed workers to date. Sensitive tests for picking up sub-clinical effects included those that measured tremor, eye-hand coordination, diadochokinesis, and finger tapping, i.e., those tests that involve repetitive simple movements over a short time. These studies found no effects on intellectual functions involving complex cognitive tasks. Neurophysiological studies are readily administered to workers in a standardized fashion, do not require special facilities for their administration, and have been accepted for the medical monitoring of workers (Crump and Rousseau, 1999). Further, they form the basis for environmental and

workplace standards for acceptable exposure levels to Mn. The relationship between results of neurophysiological testing and Mn exposure are summarized in the following table.

Table4: Neurophysiological test results vs. manganese exposure

Exposure level (mg/m ³)	Tremor	Finger tapping	Eye-hand coordination	Diadocho-kinesis	Simple reaction time	Short-term Memory	Reference
0.97 median	+		+		+	-	Roels et al., 1987a
0.215 resp. mean; 0.95 total mean	+		+		+	-	Roels et al., 1992
0.25 mean		+	-	-	+	+/-	Iregren, 1990; Wennberg et al., 1991
0.066 resp mean; 0.18 total mean	-	-	-		-	-	Gibbs et al., 1999
0.035 g.m. respirable	+	-		+	-	-	Mergler et al., 1994
0.093 mean; 0.05 resp.(calc)			-				Lucchini et al., 1997
0.057 resp. mean	-			-		-	Deschamps et al., 2001
0.017 g.m.; 0.067 mean resp.	+	+ dose-response	-		-	+	Lucchini et al., 1999
>2		-	-			-	Hua and Huang, 1991

g.m. = geometric mean

VIII. Summary

Exposures to manganese (Mn) can occur when pouring, cutting, grinding or welding steel that contains Mn. Exposures during welding have ranged from 0.024-0.22 mg/m³ in the last decade with higher exposures when there is GMAW welding, no ventilation or welding on manganese alloy steel. Mn exposures during mining or ferromanganese alloy production usually range from 0.19-3.9 mg/m³ to as high as 47-80 mg/m³ under poor ventilation conditions.

The half-life for Mn in the blood is <5 min but 37-62 days in the head (Cotzias et al., 1968). With inhalation exposure to high levels of Mn dust or fume, a considerable amount of Mn is retained in the lungs providing a depot that slowly releases Mn to the bloodstream. Mn binds with transferrin in the blood stream and this complex crosses the

blood-brain barrier binding with transferrin receptors in the brain. The latter are concentrated in the basal ganglia, the area where Mn accumulates as well. The prolonged half-life of Mn in the brain is thought to be a combination of receptor binding and continued exposures from lung depots. Mn is excreted via the bile and gut. Individuals with chronic liver disease have increased body burdens of Mn and run a risk of developing Mn-related CNS disorders. 20-50% of patients with chronic liver failure develop findings of parkinsonism associated with elevations of Mn in the blood and basal ganglia (Olanow, 2004). Individuals with chronic liver disease are at greater risk of developing manganism with workplace exposures to Mn than those with normal liver function.

Manganism is an illness that includes extrapyramidal symptoms and findings (gait disorders, dysidiadochokinesia, cogwheeling rigidity, and an expressionless face), psychiatric symptoms (hallucinations, flight of ideas, compulsive acts, verbosity, and inappropriate laughter), intentional tremor, dystonia, incoordination and a tendency to fall when walking. Manganism differs clinically from Parkinson's Disease (PD) in that dystonia (including spasmodic gait and facial grimacing) is present and instead of a pill-rolling resting tremor, when a tremor is present it is usually made worse by intentional activities. Bradykinesia and rigidity are seen in both PD and manganism. With mild manganism there may be no cognitive effects. Manganism has been seen with high-level Mn exposures when mining Mn ores or when smelting, burning or welding ferromanganese alloys. Pathological studies of the brains of workers who died with a history of manganism have shown degenerative changes of the basal ganglia, primarily of the globus pallidus but with lesser changes involving the putamen, caudate nucleus and substantia nigra. This differs from PD where the major area of damage is to the substantia nigra. Unlike manganism where symmetrical findings predominate, with PD there are asymmetrical effects on the brain that are reflected in asymmetrical findings on clinical evaluations. Manganism is not seen when exposures decrease below 0.42-0.53 mg Mn/m³ (Kim et al., 1999; Wyntner, 1962). In non-human primates, no clinical or pathological changes occur when exposures are limited to 3 mg Mn/m³ or less. Individuals who develop manganism can improve once exposure stops. With treatment with chelating agents (EDTA or PAS), reversal of neurological abnormalities can be dramatic and permanent even when treatment is first started years after exposure stops.

PD specifically involves damage to dopaminergic neurons in the substantia nigra while with manganism there is damage downstream from the nigrostriatal dopaminergic pathway. In PD where there are decreased levels of dopamine, treatment with L-dopa can result in clinical improvement. In manganism, where dopamine levels are generally normal, L-dopa is usually ineffective. Manganese, however, can accelerate the oxidation of dopamine to a neurotoxic byproduct which can damage dopamine nerve endings in a non-human primate model (Erkisson et al., 1992). This may explain those cases where L-dopa has proven useful.

Racette et al. (2001, 2005a) hypothesize that welders may develop classical PD at an earlier age, possibly because of exposure to Mn. They describe 2 case series of lawyer-referred welders with PD who appeared to have an earlier onset of PD than expected in an unselected population as well as an increased prevalence of PD. The age distribution was, however, similar to other PD populations seen in physician offices (Goldman, 2004; Semchuk et al., 1993). Further, studies of PD patient populations have not identified an

increased prevalence of either welders or exposure to Mn in these populations (Goldman, 2004; Semchuk et al., 1993; Olanow, 2004; Noonan et al., 2002; Gorell et al., 1999a, 2004; Tanner et al., 2003).

Low level exposures to Mn can result in changes in sensitive neurophysiological tests even when no changes of manganese are found on a clinical examination. Tests of eye-hand coordination, hand steadiness (tremor), and simple reaction time are frequently associated with excessive Mn exposures in ferroalloy foundries and refineries. Studies of steel welders by Bowler et al. (2003), Sinczuk-Walczak et al. (2001) and Sjogren et al. (1996) found no neurobehavioral or neurophysiological changes associated with welding. One study by Rudell et al. (1988), where CO exposure may have occurred, found smooth eye pursuit poorer in welders with worsening during welding. There was no association between welding and Mn exposure levels. CO can reach high levels (50-150 ppm) when air-arc gouging with carbon and graphite electrodes or when MAG welding with a 20% CO₂ shield gas with poor ventilation (Sjogren, 1994; Ulfvarson, 1981). Under these conditions, blood carboxyhemoglobin levels have reached as high as 20%. Exposures to CO at levels near or below these values can result in prolonged reaction times and changes of organic brain disease on neuropsychological testing. When exposure to Mn is discontinued, neurophysiological abnormalities improve or disappear (Roels et al., 1999) while with continued exposures to low levels of Mn abnormalities do not progress (Crump & Rousseau, 1999).

Although blood Mn levels correlate with indices of exposure in moderately exposed workers, levels in workers exposed near the TLV (0.2 mg/m³) are near those of unexposed workers: blood Mn may not add additional information to that of industrial hygiene studies for determining whether or not workers are adequately protected. Neurophysiological studies are used for worker monitoring (Crump & Rousseau, 1999) and results correlate with blood Mn levels (Lucchini et al., 1995, 1997; Roels et al., 1987a; Crump & Rousseau, 1999).

The study of Roels et al. (1990, 1992) of Mn exposed workers in a dry alkaline battery plant has been used to define an acceptable exposure level to Mn. This study found no effects on hand steadiness with cumulative respirable Mn exposures that averaged 0.730 mg-yr/m³ and found a minimum effect level of 0.793 mg/m³-yr. Using both published and unpublished results from this study, USEPA, WHO, Health Canada, ATSDR and ACGIH have set acceptable exposure levels as summarized in the following table.

Table 5. Acceptable levels set by various agencies

Agency	Acceptable 8 hour exposure level (µg/m ³)	Acceptable continuous exposure level (µg/m ³)	Reference
USEPA		0.050	Davis, 1999
ATSDR		0.040	ATSDR, 2000
Health Canada		31.5	Egyed et al., 1996
WHO		30	WHO, 2000
ACGIH	200		ACGIH, 2001

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