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REVIEW

# Neurological risks associated with manganese exposure from welding operations – A literature review

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## Abstract

Exposure to manganese dusts and fumes may cause a clinical neurological syndrome called manganism. Welders are frequently exposed to manganese-containing fumes generated by electric arcs and thermal torches. This paper reviews studies on the association between exposure to such welding fumes and neurological disease. Using the IRSST expert panel criteria, 78 cases of probable/possible, and 19 additional cases of possible occupational manganism were identified in the literature among manganese-exposed workers involved in welding processes. Epidemiological evidence linking welding exposures to Parkinson's disease is still controversial. Although more research is needed to clarify the risks of neurological impairment from welding, control measures including ventilation and adequate respiratory protection, should be implemented to minimize welding fume exposures. The significance of fume transport into the central nervous system via the olfactory nerve, which by-passes the blood-brain barrier, also needs to be assessed.


***Keywords:*** Welding; Manganism; Parkinson's disease; MIP; Construction trades

**Contents**



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## Introduction

Exposure to manganese (Mn) may result in a "specific clinical central nervous system syndrome" called manganism (Ostiguy et al., 2005). Manganese is a component of nearly all steels and is present in many welding rods and wires. During arc welding, it and other metals become airborne as an inhalable fume, posing a potential health hazard. As part of an ongoing research effort into construction hazards, this literature review examines the neurological risks associated with exposure to welding fumes containing Mn.

Estimates of the number of workers exposed to welding fumes range from 410,000 full-time welders to over one million workers who weld intermittently (Antonini, 2003). Within the construction industry welding and associated processes (e.g., arc-cutting) are routinely performed by pipefitters, ironworkers, boilermakers, and sheet metal workers. Other trades may also weld and perform thermal cutting of metals. This work often occurs in process vessels, such as tanks or boilers, or in other poorly ventilated settings. Engineering controls for health hazards, such as local exhaust ventilation, are rarely used on US construction sites. Given the potential for excessive exposures to welding fume, there is concern that workers may be at risk for manganism, Parkinson's disease (PD) and/or other preventable neurological disorders.

Current litigation (Wyckoff and McBride, 2004) is focusing attention on the relationship between welding, manganese exposure, and parkinsonism. Parkinsonism is a clinical syndrome characterized by tremors, rigidity, gait and balance problems, and slow movement (bradykinesia). These symptoms can be caused by neurological diseases such as PD, cerebrovascular conditions, drugs, infections, and exposure to a variety of toxic substances, including manganese (Cersosimo and Koller, 2006).

## Methods

The objective of this paper is to present a brief overview of the neurotoxicity of manganese in occupational settings, and a summary of some of the literature relating to the differential diagnosis of Parkinson's disease and manganism. The epidemiological and medical case-study literature specific to welding and neurotoxicity was examined to assess the risks of manganism and/or PD. The literature was summarized using the IRSST criteria (Ostiguy et al., 2005) for determining occupational manganism outlined in Table 1. Most of the literature did not contain sufficient information to determine if alternate diagnoses had been eliminated, and therefore only "possible" cases of manganism could be identified using strict IRSST criteria. When all other criteria of a "probable" case were documented a "probable/possible" designation was assigned. Several studies documenting neuropsychological deficits in welders were not included here due to page limitations.

**Table 1.** The IRSST classification scheme for occupational manganism.

1) A clinically *possible* case of occupational manganism:
   a. Documented identifiable source of occupational exposure to manganese.
   b. One neurological element among tremor, bradykinesia, rigidity, and postural instability.
   c. Symptoms and clinical signs of neuropsychological disturbances, mainly motor.

2) A clinically *probable* case of occupational manganism:
   a. Items from a possible case plus.
   b. Neuropsychological disturbances related to basal ganglia origin.
   c. Absence or unsustained response to L-dopa.
   d. Exclusion of other neuropsychological diseases related to basal ganglia (e.g. Parkinson's disease).

3) A clinically *definite* case of occupational manganism:
   a. Items from a probable case plus.
   b. Histopathological data (lack of Lewy bodies; preference for globus pallidus) or
   c. A normal F-Dopa PET scan would confirm manganism but an abnormal scan would not exclude manganism.

## Manganese neurotoxicity

Manganese is an essential nutrient, important in the biochemical reactions of several enzymes including manganese-dependent superoxide dismutase (Dobson et al., 2004). It plays an important role in iron metabolism, and both are required for proper brain function. Elevated levels of Mn can result in toxic neurological effects; presumably through the mechanism of oxidative stress. Inhalation is the primary route of concern for occupational health effects and solubility is the governing factor regulating absorption from the lung (EPA, 2004).

Animal studies (Oberdörster et al., 2004; Brenneman et al., 2000; Lewis et al., 2005; Tjalve and Henriksson, 1999) suggest that small particles (including manganese) deposited in the nose can be transported directly into the brain via the olfactory and/or trigeminal nerves. De Lorenzo (1970) calculated neuronal transport velocities of 2.5 mm/h for 50 nm gold particles in the olfactory nerves of squirrel monkeys using transmission electron microscopy. A more recent study (Dorman et al., 2006)

in rhesus monkeys confirms this route of exposure for manganese, and suggests that it is likely to be operative in humans as well.

Occupational manganism was first described by Couper (1837), and has been studied in a variety of industries (Levy and Nasseta, 2003). Symptoms include headache, spasms, weakness in the legs, and a characteristic psychosis with euphoria, impulsiveness, and mental confusion. As the disease progresses a range of neurological manifestations are possible including: speech disturbance, gait and balance problems, tremor and excessive salivation or sweating and other CNS dysfunction (NIOSH, 1977). There is evidence that exposure to Mn at levels lower than those observed historically can produce neurological symptoms, and the term manganese-induced parkinsonism (MIP) appears in the literature (Cersosimo and Koller, 2006; Olanow, 2004).

The EPA (2004) Inhalation LOAEL-HEC (Lowest Observed Adverse Effect Level – Human Equivalent Concentration) for manganese is 0.05 $mg/m^3$ respirable particulate, or 0.34 $mg/m^3$ total particulate. The ACGIH (2007) TLV-TWA for manganese is 0.2 $mg/m^3$ total dust and set primarily with regard to manganism. Over time the TLV-TWA for manganese has declined steadily from the 1948 to 1959 level of 6 $mg/m^3$ to its current level as evidence documented neurological effects at lower levels (ACGIH, 1992). The OSHA PEL for manganese is a 5 $mg/m^3$ ceiling limit (USDOL, 2005) and NIOSH (2005) has an REL of 1 $mg/m^3$ (8-h TWA) for most manganese compounds and fume.

## Parkinson's disease

Parkinson's disease is a progressive, idiopathic disorder that "occurs when a group of cells, in an area of the brain called the substantia nigra, that produce a chemical called dopamine begin to malfunction and eventually die" (Parkinson's Disease Foundation Website: downloaded 5/1/04). Symptoms include: (1) tremors in the extremities, jaw, and face, (2) stiffness of the limbs and trunk; (3) slowness of movement, and (4) impaired balance and coordination. The peak age of onset is about 60 (Cersosimo and Koller, 2006). Although the contribution of genetics to the overall incidence of PD is thought to be relatively small, further research is needed (Checkoway and Nelson, 1999). Parkinson's disease progresses through stages with ongoing development of Lewy bodies within nerve cells (Braak et al., 2003). Lewy bodies consist primarily of "a misfolded protein alpha-synuclein", which gives up its ability to bind with membranes and folds into pathological inclusions. In addition 80–90% of PD patients have significant olfactory dysfunction (Muller et al., 2002; Wenning et al., 1995).

Hawkes et al. (1999) note that the odors most misidentified by PD patients, when using the University of Pennsylvania Smell Identification Test, were lemon, pizza, wintergreen, rose, and clove. They suggest that PD may start in the olfactory brain prior to damage in the basal ganglia. Duda et al. (1999) have shown that alpha-synuclein, is abundant in the olfactory epithelium of humans and that it may play a role in the function of neurons exposed to the external environment.

## Differential diagnosis of PD and manganism

Work by Cersosimo and Koller (2006) and Olanow (2004) summarize the differences that help differentiate MIP from PD. In general, PD patients show better response to L-dopa than do those with MIP. The T1-weighted MRI scan in PD patients is normal, while in the case of manganese toxicity the scan shows "high signal change in GP (globus pallidus), striatum and SNr bilaterally" (Olanow, 2004). Flurodopa PET scans are normal in the case of manganese toxicity, but for PD there is decreased striatal uptake in the posterior putamen (Olanow, 2004). Clinical features more common with manganism than with PD include: early onset (less than 60 years of age), kinetic tremor (a resting tremor is more common in the PD individual, which is typically asymmetric), postural instability and gait problems, speech and mental abnormalities may be prevalent early in the disease, and symmetric clinical signs (Cersosimo and Koller, 2006).

In 2002, the IRSST, a non-profit Canadian research group, convened an expert panel to establish a definition and classification scheme for occupational manganism. The report includes guidance for the differential diagnosis of PD and manganism, and a methodology to classify cases of occupational manganism. Table 1 reproduces this classification scheme. The panel states that "a clinical picture of parkinsonism with no response to levodopa and a normal F-dopa PET scan strongly suggests a diagnosis of manganese induced parkinsonism" (Ostiguy et al., 2005). A more definitive test is the post-mortem histopathology examination. The lack of Lewy bodies in manganism and the preference for damage to the globus pallidus (GP) is in contrast to Parkinson's disease where there are generally Lewy bodies, degeneration of the nigrostriatal pathways, and loss of striatal dopamine (Ostiguy et al., 2005).

## Welding overview

Welding is a technique for joining metals by heating them to a high enough temperature to cause fusion. The methods to accomplish this encountered most often in

industry employ an electric arc, or a gas flame. The base metals to be welded are very often some type of steel, and the filler metal is often an electrode or wire. The composition of the base metals, the electrode and/or filler wires is important in determining the fume make-up, and very often manganese is present.

Several different types of welding are employed depending upon a variety of factors. However, in construction, shielded metal arc welding (SMAW or stick) is the predominant process, with gas metal arc (GMAW or MIG) and gas tungsten arc (GTAW or TIG) welding used for special applications. Flux-cored arc welding (FCAW) may also be used, but is less common, than stick welding. The type of welding is important with regard to determining the fume composition and generation rate, which together with ventilation patterns will govern the exposure. An excellent summary of the various types of welding, and the associated hazards can be found in Burgess (1995).

In addition to these techniques there are the related operations of arc air cutting, gouging, plasma cutting and oxyacetylene torch cutting (OXY). These are similar to arc welding in many respects, but differ in having higher generation rates of fume and hence greater risks of over exposure to fume components (Burgess, 1995). Construction workers and others often perform these tasks in addition to arc welding and hence identifying someone as a ''welder'' may be rather imprecise in terms of exactly what the exposures are. A prior review on arc welding and manganism (McMillan, 2005) separated arc welders from those involved with these related cutting operations; our choice is to include them here.

## Studies of neurotoxicity pertinent to welding

The studies reviewed below are presented in two subsections, and the results are summarized in Tables 2 and 3, respectively. The first section concerns recent epidemiological studies investigating the relationship between PD and welding. In some cases other neurological diseases are also reported. The second section presents case studies that include possible or probable cases of manganism.

## Epidemiological studies: Parkinson's disease and welding

A recent review on the epidemiology of Parkinson's disease (De Lau and Breteler, 2006) summarizes the methodological limitations of studies seeking to establish causal associations between exposures and Parkinson's disease. Perhaps the most important being uncertainties in clinical diagnosis and ''the lack of universally accepted criteria for PD…'' In addition they observe that ''the critical time period during which patients are at risk of PD is unknown, and therefore whether early, late, cumulative or average lifetime exposures should be studied is unknown.'' Dick et al. (2007) present an analysis indicating the limitations of job titles as risk factors for PD in epidemiological studies. They conclude ''In contrast to retrospective exposure assessment, job or industrial sector is a weak indicator of toxic exposures such that true associations may be missed.''

The studies described in this subsection are summarized in Table 2. A ''+'' or ''−'' symbol in a column of Table 2 indicates a positive or negative finding of an association between welding and the neurological disease (PD or other). An ''NR'' (not reported) indication means that no such association either positive or negative was reported. If possible an odds ratio (OR) and confidence interval (CI) are noted and further information is given in the ''Comments'' column.

In a large case-control study (Park et al., 2005) over 2 million death certificates from 1992 to 1998 in 22 states

**Table 2.** Epidemiological studies reporting a positive (+) or negative (−) association for welding and Parkinson's disease and other neurodegenerative diseases.

| Reference | Parkinson's disease | Comments | Other neurodegenerative diseases |
|---|---|---|---|
| Park et al. (2005) | + | OR = 1.77 CI (1.08–2.75) | – |
| Fryzek et al. (2005) | − | Danish, stainless-steel welding | – |
| Fored et al. (2006) | − | Swedish, welders and flame cutters | – |
| Racette et al. (2001) | + | Early onset PET scans typical of PD | NR |
| Racette et al. (2005) | + | Excess prevalence | NR |
| Goldman et al. (2005) | +/− (included parkinsonism) | Early onset | NR |
| Marsh and Gula (2006) | − | Flux cored and submerged arc | – |
| Gorell et al. (2004) | + | Mn and other metals associated | – |

NR = not reported.

**Table 3.** Studies of welders with cases of occupational manganism according to IRSST [2005] criteria.

| Reference | Job descriptions | Manganism classification | Manganese exposures range ($mg/m^3$) |
|---|---|---|---|
| Barrington et al. (1998) | Gouging, welding railroad | Prob/Poss (1) Possible (1) | 0.002[a]–4.29 |
| Bowler et al. (2006b) | Welder | Prob/Poss (1) | NR |
| Bowler et al. (2006a) | Welders | Prob/Poss (38) | NR |
| Bowler et al. (2007a, b) | FCAW and SMAW welding | Prob/Poss (11) | 0.006–0.312 |
| Chandra et al. (1981) | Fabrication, rails, ship repair | Possible (5) | 0.44–2.6 |
| Crossgrove and Zheng (2004) | Construction | Possible (8) | $\leqslant$25.7 |
| Discalzi et al. (2000) | Welding and electrode fixing | Prob/Poss (1) | NR |
| Franek (1994) | Railroad, steel fabrication | Possible (1) | 0.32 and 0.73 (2 welders) |
| Hernandez et al. (2006) | Welders | Prob/Poss (5) | NR |
| Hine and Pasi (1975) | Burning | Prob/Poss (1) | NR |
| Josephs et al. (2005) | MIG, TIG stainless, galvanized | Prob/Poss (3) Possible (3) | NR |
| Koller et al. (2004) | Welder | Prob/Poss (13) | NR |
| Ono et al. (2002) | Welder | Possible (1) | NR |
| Sadek et al. (2003) | Shipyard welding | Prob/Poss (1) | NR |
| Tanaka and Lieben (1969) | Arc burning | Prob/Poss (1) | 1.3–20.13 |
| Whitlock et al. (1966) | Arc burning | Prob/Poss (2) | 0.1–4.7 |
| Ellingsen et al. (2006) | Welders | Poss (27)? | 0.003–4.62 |

NR = not reported.
[a]In respirator.

were examined to ascertain the relationship between mortality from four neurodegenerative diseases and occupation. The diseases examined included Parkinson's disease, Alzheimer's (AD), presenile dementia, and motor neuron disease. The authors examined the *a priori* hypothesis that PD was associated with welding. The categories of workers identified as welding were: welders and cutters, boilermakers, structural metal workers, millwrights, plumbers, pipefitters, and steamfitters. The study concluded, in part, that of the four diseases examined "only PD was associated with occupations where arc welding of steel is performed and only for the 20 PD deaths below age 65" (Park et al., 2005). The authors calculated the mortality odds ratio for the 20 deaths at 1.77 with 95% CI = 1.08–2.75. Study limitations included the lack of control for smoking and possible interactions between socio-economic status and job title.

A retrospective cohort study of PD and other neurodegenerative diseases in Danish stainless-steel welders failed to produce any compelling associations (Fryzek et al., 2005). The study involved over 27,000 welders, but did not include a meaningful exposure assessment. The cohort was initially selected for a lung cancer study and excluded shipyard welding, the authors acknowledged the limitations and state "welders in our cohort may have been less exposed because exposure levels are lower in stainless-steel welding and high level exposure environments like shipyards were left out of the cohort. Therefore rates for PD found for welders in the present study may not necessarily be representative…" (Fryzek et al., 2005).

In a large study of welders ($n = 49{,}488$) in Sweden (Fored et al., 2006) the investigators did not detect an increased rate for PD or any other basal ganglia or movement disorders among welders and flame cutters when compared to an age and area matched cohort of employed men ($n = 489{,}572$). The overall adjusted rate ratio (aRR) was 0.91 with a 95% C.I of 0.81–1.01, the adjusted rate ratio for Parkinson's disease was 0.89 (95% CI 0.79–0.99). The authors noted that "rates for Parkinson's disease among welders in shipyards, where exposures to welding fumes are higher, were also similar to the general population (aRR = 0.95; 95% CI 0.70–1.28)" (Fored et al., 2006).

Gorell et al. (2004) looked at 10 variables that had been independently associated with Parkinson's disease from previous case-control studies, and examined them jointly. Of the 10 variables, the highest adjusted odds ratio was for exposure to manganese for greater than 20 years with an adjusted odds ratio of 10.63 (95% CI = 1.07–106). Exposure to copper for greater than 20 years was the next highest with OR = 2.49 (95% CI = 1.06–5.89). The authors developed a multivariate model that included 4 variables accounting for 54% of the population attributable risk. The variables were smoking less than 30 years (protective effect), PD in relatives, occupational insecticide exposure, and occupational exposure to copper and lead jointly for greater than 20 years.

Two epidemiological investigations (Racette et al., 2001, 2005) have provided some associations between welding and Parkinson's disease. In the earlier study the authors attempted to determine if welding-related parkinsonism differed from PD by using a case-control study with 15 career welders compared against two control groups with PD. One control group was assessed sequentially to monitor clinical features, while the second control group was sex and age matched to compare the frequency of motor fluctuations. They found a statistically significant difference in the age of onset for Parkinson's disease between the welders (46 years) and the first control group (63 years). Two welders had PET scans with flurodopa typical for PD and all welders responded to levodopa. None of the welders had MRI-identified abnormalities in the basal ganglia. The authors concluded that welding may be a risk factor for Parkinson's disease and that a genetic contribution to susceptibility in the exposed individuals was possible. The potential for referral bias, and positive family histories for PD, have been raised as limitations of the study (Ravina et al., 2001).

In the latter study, Racette et al. (2005) reported on the prevalence of parkinsonism in 1423 welders in Alabama. They estimated the prevalence of parkinsonism among active male welders using strict and liberal definitions from 977 to 1335 cases per 100,000 population. This was higher than for the age-adjusted general population, with a prevalence ratio of 10.19 (95% CI = 4.43–23.43). The author's acknowledged the potential for bias in the assessment since the reviewers knew that the subjects were welders.

Goldman et al. (2005) reviewed medical records from 2249 patients diagnosed with parkinsonism or PD and compared job frequencies with regional Department of Labor frequencies. They found physician, dentist, farmer and teacher professions more common than expected in the PD/parkinsonism group. Welders, who were not overly common in this group (only 3 welders were in the study), had a significantly earlier age of disease onset, 54.7 years vs. the overall mean of 62.5, the odds ratio was significant ($p<0.05$) at 2.3. This is consistent with the observations of Racette et al. (2001). Limitations included potential referral bias, misclassification of occupation, and confounding due to smoking. A pilot study of occupational and environmental risk factors for Parkinson's disease (Weschler et al., 1991) was inconclusive, but suggested that farming, welding, and occupational metal exposures, particularly aluminum, warranted further investigation.

Contrary to the above, however, a recent case-control study (Marsh and Gula, 2006) reported no association between employment as a welder and "Parkinson disease, parkinsonism or a related neurological disorder." They examined 12,595 individuals who were employed between 1976 and 2004. The welding was done on primarily mild steel using electrode welding, flux-cored arc welding, gas welding and submerged arc welding. The study did not include an assessment of smoking histories. Exposure misclassification is a potential limitation given the very different exposure profiles associated with the different types of welding, and uncertainty over the exposures to the cases.

## Studies: manganism and welding

The IRSST criteria described in Table 1, for categorizing clinical cases of occupational manganism, are applied here to cases described in the literature. Designation of a "possible" case of occupational manganism requires all three IRSST criteria, (i.e., items 1a–c on Table 1); while designation as a "probable/possible" case requires all the conditions for a "possible" case (item 2a on Table 1) plus at least two additional items from 2b, 2c, or 2d. This classification suggests there is a continuum from possible to probable. References presented in this subsection are summarized in Table 3.

Whitlock et al. (1966) report manganese poisoning in two individuals involved in an arc-burning operation on manganese-containing steel castings. The operation was performed in an enclosed, unventilated booth. Air samples indicated a range of airborne Mn exposures of 0.1–4.7 $mg/m^3$ without ventilation, and 0.1–2 $mg/m^3$ after installation of a local exhaust system. Both individuals exhibited bradykinesia, muscle weakness, gait and balance problems, and other symptoms indicative of manganese toxicity. Chelation therapy and removal from exposure resulted in improved symptoms. Shortly thereafter, Tanaka and Lieben (1969) reported a third case of manganese poisoning from this same operation and facility, after ventilation had been installed. The individual developed symptoms including rigidity and gait problems, among others, within about 1 year of work. Airborne manganese concentrations measured in 1968 ranged from 1.3 to 20.13 $mg/m^3$ with a mean of 8.59 $mg/m^3$. Chelation therapy and removal from work resulted in improved symptoms.

Hine and Pasi (1975) report a case of manganism in a welder whose primary job was "to burn off metal projections from manganese steel castings." The patient presented with an intention tremor (a tremor triggered by aiming for a target), depression, increased muscle tone, and gait and posture problems; deep reflexes were normal. Chelation and removal from exposure led to improvement.

Barrington et al. (1998) described manganese toxicity in 5 welders and 3 other workers involved in frog shop repairs of railway track. Subject 1 was an index case of manganese encephalopathy originally diagnosed by Nelson et al. (1993) with dementia, intention tremor,

balance problems, and increased T1-weighted signals on MRI. Of the remaining 4 welders all but one reported dizziness, and subject 2 exhibited an intention tremor and increased sway on platform testing. Other neuro psychological symptoms were observed in the welders including mood and affect. Three of the welders including subject 1 were engaged in arc air gouging (either indoors or out) and grinding and finishing railway connectors containing 11–15% manganese steel. The remaining 2 welders performed various tasks in the vicinity of manganese-containing fumes, but not primarily in the frog shop.

Six personal samples for manganese exposure indoors had been collected on the frog shop personnel prior to diagnosis of the index case. The mean exposure was 0.67 mg/m$^3$ with a standard deviation of 0.22 mg/m$^3$. Subsequent to the diagnosis of the cases a "cantilevered exhaust fan was installed for all indoor welding" (Barrington et al., 1998) and 6 additional indoor personal samples were collected with a slightly reduced mean of 0.57 mg/m$^3$ and standard deviation (SD) of 0.25 mg/m$^3$. Nine personal outdoor samples showed a mean of 1.24 mg/m$^3$ and standard deviation of 0.52 mg/m$^3$. Sample times ranged from 11 to 410 min, 67% of all personal samples exceeded 0.2 mg/m$^3$ and 29% exceeded 1.0 mg/m$^3$. The range of values was 0.002 mg/m$^3$ inside a PAPR respirator on a worker doing arc air processes outside, to 4.29 mg/m$^3$ for welding outdoors. Based on these results Subject 1 is classified as a probable case of occupational manganism and Subject 2 a possible case.

Chandra et al. (1981) explored manganese toxicity in 20 welders at each of three different plants (A–C) and 20 matched, but unexposed controls, for a total of 80 different individuals. Airborne concentrations of manganese ranged from 0.44 to 2.6 mg/m$^3$ and positive neurological signs (the presence of brisk reflexes and tremors) were recorded. The mean air concentration and the average duration of work (approximate cumulative exposure) correlated reasonably well with the incidence of neurological signs at the plants. The overall symptom pattern and the correlation between serum calcium and neurological signs led the authors to conclude that "it may be assumed that these welders were suffering early manganese poisoning."

Discalzi et al. (2000) present a case report of a welder with postural tremor, muscular hypertonia, and bradykinesia. The individual had worked for approximately 31 years as a welder using manganese-containing rods and wires. Elevated signal intensities in the globi pallidi and substantia nigra on T1-weighted MRI suggested metal deposition in the basal ganglia. The patient had poor response to L-dopa, but showed clinical improvement after cessation of exposure and chelation therapy. A subsequent reduction of the MRI signal intensities was observed. The diagnosis of parkinsonism due to manganese exposure was made.

Sadek et al. (2003) present a case report for a 33-year-old male with a history of "progressive cognitive slowing, rigidity, tremors, slowing of movements and gait instability." They noted that levodopa was unhelpful in treatment, and that increased signal intensity on the T1-weighted MRI in the bilateral basal ganglia was present. The patient was a welder (for 3 years) on steel–manganese alloy, did not use a respirator and worked in a confined ship's hold. The authors concluded that "…welding can produce enough exposure to manganese to produce neurologic impairment" (Sadek et al., 2003).

Bowler et al. (2006a) studied 47 welders with clinical histories of manganese exposure compared to a convenience sample of 42 unexposed controls. Neuropsychological testing showed important dose–effect relationships. The authors cited odds ratios indicating "highly elevated risk for neurological symptomology of manganism" and very high odds ratios for mood disturbances like anxiety, depression, and confusion. Symptoms with estimated adjusted odds ratios (in parentheses) that were significant, $p<0.001$ included: neurological (2.9), memory concentration (2.6), anxiety (3.6), depression (4.3), sleep disorder fatigue (2.9), headaches and chemical sensitivity (2.3), visual (2.7), sensory (3.4), and dermatological (4.9). Neurological exams indicated 80.9% of the cases exhibited tremor, and 36.2% had bradykinesia. Based on this data an estimated 38 cases of probable/possible manganism existed in the cohort.

A case study by Bowler et al. (2006b) describes a 33-year-old male welder presenting with tremors, bradykinesia, rigidity, cock-walk gait, and cognitive difficulties. Treatment with L-dopa was unhelpful. Serum and urine manganese levels were elevated and MRI scans revealed increased T1-weighted signal intensities in the globus pallidus. The individual had welded for 3 years, primarily on mild steel, but did so in enclosed spaces in a shipyard usually without respiratory protection. He noted ventilation was not used very often and stated "about 30% of the time there might have been local exhaust or dilution ventilation, but they were mostly malfunctioning" (Bowler et al., 2006b). Deficits in cognitive flexibility, information processing, and motor speed, as well as anxiety, irritability, and depression with psychotic features were noted. Early-onset MIP was diagnosed.

Bowler et al. (2007a) evaluated 43 welders engaged in the reconstruction of the San Francisco Bridge. From this group 11 were identified as cases of manganism based on work history, self-reported symptoms and a neurological exam. The neurological exam required at least one asymmetric symptom from resting tremor, rigidity or bradykinesia; and 2 or more on two different Unified Parkinson's Disease Rating Scale (UPDRS) motor areas: rest tremor, rigidity, bradykinesia or postural instability. A cumulative exposure index for

manganese was constructed from airborne concentration measurements and work histories including information on the time spent using different types of welding (flux cored or stick). The authors concluded that the neuropsychological test results "contribute in a dose–effect related way to the portrait of manganism" (Bowler et al., 2007a). Further neurological, neuropsychological and pulmonary function testing results for San Francisco Bridge welders were reported in Bowler et al. (2007b). Statistically significant dose-effect relationships were reported for cumulative Mn exposures and lower IQ, sexual dysfunction, fatigue, depression, and headache.

Koller et al. (2004) examined 13 male welders with an average age of 61.5 years (±14.7) all had a history of welding with an average exposure duration of 25.2 years (±14.3). Several identified working in confined spaces without adequate ventilation, all exhibited bradykinesia, most had kinetic tremor, postural instability, and symmetrical signs, and none exhibited dystonia. The authors conducted a double-blind, randomized, placebo-controlled trial to assess the efficacy of levodopa on manganese-induced parkinsonism. They concluded the therapy was not effective for the welders and that the L-dopa unresponsiveness might be useful to distinguish PD from MIP.

Josephs et al. (2005) examined eight male welders who were diagnosed with neurotoxicity from welding fumes. "All performed metal inert gas or tungsten inert gas (Case 2 only) welding, usually welding stainless steel or galvanized steel." Lack of ventilation and/or work in confined spaces was reported by all welders none of whom wore personal respirators. Welding durations were from 1 to 25 years prior to the development of the first neurological symptoms. All welders had increased T1 basal ganglia signal on MRI. Six of the eight welders exhibited tremor and 5 out of 8 had balance problems. The neurological symptoms included predominantly parkinsonism in three of the welders, "multifocal myoclonus and limited cognitive impairment" in two welders, two others with vestibular–auditory dysfunction, and one with anxiety and sleep apnea. Three welders were treated with L-dopa with limited results. The authors conclude that welding without protection was associated with the syndromes observed and Mn toxicity may have been responsible.

An investigation by Ono et al. (2002) specifically associated neurotoxic effects with exposure to manganese in welding fume by citing myoclonic involuntary movements in the right upper and lower extremities of a 17-year-old welder. The authors noted elevated levels of manganese in the blood and hair and the typical high-intensity signals in the globus pallidus on T1-weighted MRI. Chelation therapy was useful in improving the symptoms and MRI results. The individual had welded for about 2 years, no exposure data were presented.

Hernandez et al. (2006) presented follow up data on 7 workers who had been diagnosed with MIP and treated by removal from exposure and chelation therapy. Five of the workers were welders. They noted that anti-parkinsonian drugs, including L-dopa were ineffective in the treatment of their patients. Symptoms included parkinsonism, and postural intentional tremor in all 5 welders and muscle rigidity and bradykinesia in most of them. Airborne exposure concentrations to manganese were not presented but duration of exposures for the welders ranged from 8 to 31 years. The therapy resulted in improvement in 5 of the 7 workers and 4 of the 5 welders.

Franek (1994) reported on two welders. The first performed wire-fed, argon gas welding on fabricated steel beams containing between 0.05 and 2 percent manganese. The welding was done in a 100,000 $ft^3$ shop with no local exhaust. Full shift sampling revealed an exposure of 14 $mg/m^3$ to total fume with the Mn level at 0.73 $mg/m^3$, well in excess of the TLV. The second welder was involved with welding railroad "frog" sections using sticks with 2–25% manganese. The welder had worked on the railroad tracks since 1983 and used no respiratory protection until 1992. The welder developed symptoms of manganism within 9 years. The second welder had two short-term samples; one was reported as a 15 min TWA for Mn at 7.2 $mg/m^3$ and a second sample of 12 min with a TWA of 4.0 $mg/m^3$ for manganese. The equivalent 8-h TWA of 0.325 is over 50% above the TLV assuming no exposure for the rest of the day.

In a cross-sectional study of 96 welders and 96 controls Ellingsen et al. (2006) reported exposures to airborne Mn ranging from 0.003 to 4.62 $mg/m^3$. The study also included 27 patients who were former welders and had been diagnosed with manganism. In a subsequent paper (Ellingsen et al., 2008) neurobehavioral testing was conducted on these individuals. The patients who had been diagnosed with manganism showed "no alterations in hand tremor as assessed by the CATSYS system." Neither paper presented sufficient detail to apply the IRSST criteria, although clear neurological impairments were demonstrated, especially for impaired Finger Tapping speed and Grooved Pegboard performance (Ellingsen et al., 2008).

## Concluding remarks

Exposure to manganese dust and fumes can produce a specific neurological disease called manganism. However, the level of exposure required to produce the disease will vary from individual to individual. Welders are exposed to Mn at different levels, but studies demonstrate they are frequently exposed at levels well

in excess of the current TLV®-TWA of 0.2 mg/m$^3$. Based on the literature reviewed here 78 'probable/possible' cases of occupational manganism were identified in welders using criteria established by the IRSST expert panel. An additional 19 cases were classified in the 'possible' category.

There is evidence that the difference between manganism and Parkinson's disease can be discerned clinically. However, better definitions are needed to minimize misdiagnosis. The role that manganese or other agents associated with welding might play in the causation of PD remains unknown. Evidence suggests that genetic factors, iron intake, and exposure to other agents may be important in this association. Welders are inevitably exposed to high levels of iron along with manganese, and the combined interaction of these two metals (and others) needs further study. Research is also needed on the role of olfactory nerve transport into the brain for manganese, iron, and other metals in welding fume. This seems compelling given the fact that the initial pathology for PD may originate in the olfactory bulb, and that the blood-brain barrier is circumvented by this exposure route.

This review suggests that welders are at risk of manganism from arc welding and thermal cutting operations. The type of welding is especially critical in determining the exposures. The exposure to Mn will increase when the Mn content in the base metals and/or welding rods is high (e.g., railroad steel), when the electrode current densities are high (e.g., arc air cutting), when the arc time is high (actual welding vs. set up time), and when there is poor ventilation (e.g., enclosed spaces). Within the construction industry boilermakers, pipe fitters, and iron workers may be at the greatest risk, particularly when welding in enclosed, poorly ventilated spaces.

Local exhaust ventilation (LEV) may be only partially effective at reducing exposures and field-based research is needed to document and improve its effectiveness. Supplying effective ventilation for welding and related processes on complicated construction work sites requiring mobility and flexibility is challenging. Worker education and training will be important in achieving successful control in conjunction with engineering interventions. Using welding techniques that reduce fume generation e.g., replacing flux-cored welding with other forms when possible, and/or reducing current densities, may be a fruitful approach as well. When engineering controls are not possible, or are ineffective, adequate respiratory protection must be provided.

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