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State-of-the-Science Review: Does Manganese Exposure During Welding Pose a Neurological Risk?

Annette B. Santamaria [a], Colleen A. Cushing [b], James M. Antonini [c], Brent L. Finley [d] & Fionna S. Mowat [e]

[a] ENVIRON International Corporation, Houston, Texas, USA

[b] Exponent, Chicago, Illinois, USA

[c] National Institute for Occupational Safety and Health (NIOSH), Morgantown, West Virginia, USA

[d] ChemRisk, San Francisco, California, USA

[e] Exponent, Menlo Park, California, USA

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STATE-OF-THE-SCIENCE REVIEW: DOES MANGANESE EXPOSURE DURING WELDING POSE A NEUROLOGICAL RISK?

Annette B. Santamaria[1], Colleen A. Cushing[2], James M. Antonini[3], Brent L. Finley[4], Fionna S. Mowat[5]

[1]ENVIRON International Corporation, Houston, Texas, [2]Exponent, Chicago, Illinois, [3]National Institute for Occupational Safety and Health (NIOSH), Morgantown, West Virginia, [4]ChemRisk, San Francisco, California, and [5]Exponent, Menlo Park, California, USA

Recent studies report that exposure to manganese (Mn), an essential component of welding electrodes and some steels, results in neurotoxicity and/or Parkinson's disease (PD) in welders. This "state-of-the-science" review presents a critical analysis of the published studies that were conducted on a variety of Mn-exposed occupational cohorts during the last 100 yr, as well as the regulatory history of Mn and welding fumes. Welders often perform a variety of different tasks with varying degrees of duration and ventilation, and hence, to accurately assess Mn exposures that occurred in occupational settings, some specific information on the historical work patterns of welders is desirable. This review includes a discussion of the types of exposures that occur during the welding process—for which limited information relating airborne Mn levels with specific welding activities exists—and the human health studies evaluating neurological effects in welders and other Mn-exposed cohorts, including miners, millers, and battery workers. Findings and implications of studies specifically conducted to evaluate neurobehavioral effects and the prevalence of PD in welders are also discussed. Existing exposure data indicate that, in general, Mn exposures in welders are less than those associated with the reports of clinical neurotoxicity (e.g., "manganism") in miners and smelter workers. It was also found that although manganism was observed in highly exposed workers, the scant exposure-response data available for welders do not support a conclusion that welding is associated with clinical neurotoxicity. The available data might support the development of reasonable "worst-case" exposure estimates for most welding activities, and suggest that exposure simulation studies would significantly refine such estimates. Our review ends with a discussion of the data gaps and areas for future research.

It has been known for several decades that chronic exposure to elevated airborne levels of manganese (Mn) in mining and manufacturing settings is associated with an increased risk of certain neurological effects (Rodier, 1955; Tanaka & Lieben, 1969; Huang et al., 1989, 1998; Roels et al., 1987a, 1992; Wang et al., 1989; Mergler et al., 1994; Hochberg et al., 1996; Bader et al., 1999). In the last 30 yr, questions have been raised regarding a possible causal association between neurological effects in welders and the use of Mn-containing consumables (e.g., electrodes and wires). Although it is estimated that there are more than 1 million welders worldwide, the question of whether there is an increased risk of neurotoxicity in welders as a result of Mn exposure is still unanswered. While some investigators concluded that the current clinical, toxicological, and epidemiological evidence does not support the existence of such a relationship, others suggested that welding is a risk factor not only for nonspecific neurological symptoms, but also for the accelerated onset of Parkinson's disease (PD).

During the last 100 yr, only approximately 15 case reports have been published in the medical literature describing clinical neurological symptoms in welders (Belniker, 1932, as cited in Fairhall & Neal, 1943; Whitlock et al., 1966; Tanaka & Lieben, 1969; Rasmussen & Jepsen, 1987; Wang et al., 1989; Nelson et al., 1993; Franek, 1994; Barrington et al., 1998; Kim et al., 1998; Sato et al.,

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Dr. Finley has testified as an expert witness, in cases involving alleged asbestos exposures during welding rod use.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Address correspondence to Annette B. Santamaria, ENVIRON International Corporation, 10333 Richmond, Suite 910, Houston, TX 77042, USA. E-mail: asantamaria@environcorp.com

2000; DiScalzi et al., 2000; Ono et al., 2002; Sadek et al., 2003; Koller et al., 2004; Josephs et al., 2005; Kenangil et al., 2006). The numerous epidemiological studies that have been conducted on welders over the last half century focused primarily on evaluating respiratory health effects; only a few cross-sectional studies or reviews evaluated neurological or neurobehavioral effects (Chandra et al., 1981; Anatovskaia 1984; Yim et al., 1998; Järvisalo et al., 1992; Sjögren et al., 1990, 1996; Jin et al., 1999; Moon et al., 1999; Korczynski 2000; Luse et al., 2000; Sińczuk-Walczak et al., 2001; Bowler et al., 2003, 2006a, 2007; Lees-Haley et al., 2004, 2006; Finley & Santamaria, 2005; Halatek et al., 2005; Racette et al., 2005; Fryzek et al., 2005; Antonini et al., 2006; Martin 2006; Park et al., 2006; Fored et al., 2006).

This article provides a comprehensive "state-of-the-science" review of the potential neurological health hazards associated with Mn exposure in various occupational cohorts. General information regarding (1) recommended intake levels of Mn and potential routes of exposure, (2) animal toxicology studies, (3) knowledge obtained from studies in humans, and (4) differences and similarities between "manganism"[1] and PD are discussed. Particular emphasis is given to studies that evaluated neurological effects in welders and other Mn-exposed cohorts. This review summarizes the regulatory history of occupational Mn exposures over the last 100 yr, including a discussion of federal limits and other occupational guidelines. A summary of the data gaps and research needs regarding welding and potential Mn-related neurological effects is also provided.

GENERAL BACKGROUND ON MANGANESE

Mn is an essential nutrient for both humans and animals, and is required for growth, development, and maintenance of health. Mn is necessary for a multitude of functions, including skeletal system development, energy metabolism, activation of certain enzymes, nervous system function, and reproductive hormone function, and is an antioxidant that protects cells from damage due to free radicals (Agency for Toxic Substances Disease Registry [ATSDR], 2000; National Research Council [NRC], 1989; U.S. Environmental Protection Agency [EPA], 1996). The most important source of Mn for the general population is diet, with most daily intakes falling below 5 mg Mn/kg (Aschner et al., 2005). The average intake of Mn from food ranges from 0.7 to 10.9 mg/d, and residents in some areas may consume an additional 3 to 5 mg/d from drinking water (Greger, 1999). In addition, vitamin and mineral supplements may contain 1 to 20 mg Mn/tablet (Aschner et al., 2005). The Food and Nutrition Board of the NRC determined that insufficient information exists to develop a recommended daily allowance (RDA) for Mn, but sufficient information is available to provide an estimated safe and adequate daily dietary intake (ESADDI). The ESADDI for adolescents and adults ranges from 2 to 5 mg/d. For infants and children up to age 10, the ESADDI ranges from 0.3 to 3 mg/d, depending on age (NRC, 1989). However, intakes up to 9 mg/d were reported to be nontoxic, and the U.S. EPA oral reference dose of 0.14 mg/kg-d is equivalent to 10 mg/d for a 70-kg person (U.S. EPA, 1996). Only a few instances of Mn deficiencies were reported in humans, with symptoms including dermatitis, slowed growth of hair and nails, decreased serum cholesterol levels, and decreased levels of clotting proteins (ATSDR, 2000).

Mn occurs naturally and is found in rocks, soil, water, and food. Mn exists as both inorganic and organic compounds, with the inorganic form being the most common in the environment. Organic compounds of Mn are used as fuel additives (methylcyclopentadienyl manganese tricarbonyl, MMT), fungicides (e.g., maneb and mancozeb), and as a contrast agent in magnetic resonance imaging. This review focuses on inorganic forms of Mn, because this is the form found in welding fumes.

Routes of Exposure

Humans may be exposed to inorganic Mn via ingestion and inhalation of ambient airborne particulates in the environment or workplace. Dermal exposures are considered to be negligible,

[1]"Manganism" is a syndrome characterized by a mask-like face, fine tremor of the hands or gross rhythmical movements of the arms and legs, emotional disturbances, and a gait described as a "cock-walk" associated with exposure to manganese.

because inorganic Mn does not penetrate the skin to any significant degree (ATSDR 2000). Mn is present in food, with the highest concentrations typically found in nuts, cereals, grains, and tea; it is also present at low levels in drinking water (NRC 1989). The oral route is considered to be less important than inhalation, because Mn is poorly absorbed from the gastrointestinal tract and Mn levels in the brain and other tissues remain relatively constant despite large fluctuations in dietary intake (Davis, 1998). Gastrointestinal absorption of Mn is approximately 3%–5% (ATSDR, 2000; Santos-Burgoa et al., 2001).

A few studies demonstrated adverse neurological effects following the ingestion of high levels or chronic exposure to Mn (Kawamura et al., 1941; Kondakis et al., 1989; Keen et al., 1999; ATSDR, 2000). In Japan, high levels of Mn in drinking water were associated with neurological symptoms such as mask-like face, muscle rigidity, muscle tremors, and mental disturbance in six families (Kawamura et al., 1941). The elevated Mn levels in water were thought to be due to leaching from batteries near the well. Several confounding factors—including rapidity of onset and recovery from symptoms before Mn levels in the drinking water had decreased—weaken the association of the symptoms with Mn in this study. A study of elderly residents in two small towns in Greece suggested an increased prevalence of neurological effects associated with the chronic intake of drinking water containing elevated levels of Mn (Kondakis et al., 1989). However, there were several limitations in this study, including a lack of dose-response data, lack of details regarding which neurological symptoms were increased in the affected population, and incomplete information regarding the group used as a control population. Other drinking water studies have failed to detect elevated levels of adverse neurological effects. For example, a cross-sectional study in Germany found that adults who were exposed for 10–40 yr to well water that contained elevated Mn concentrations did not display any adverse neurological or hepatic effects compared to the matched controls that were exposed to lower levels of Mn in drinking water (Vieregge et al., 1995). Clinical Mn neurotoxicity has been reported in patients receiving long-term parenteral nutrition and in patients with chronic liver dysfunction or renal failure, as a result of their inability to eliminate and clear Mn from the blood (Nagatomo et al., 1999; Ikeda et al., 2000; Mirowitz et al., 1991; Pal et al., 1999; Spahr et al., 1996).

The primary sources of airborne Mn in nonoccupational settings are industrial emissions (e.g., foundries), combustion of fossil fuels, and reentrainment of soils containing Mn (Hudnell, 1999; Mergler et al., 1999; ATSDR, 2000; Bolte et al., 2004). Higher inhalation exposures may be experienced in occupational settings such as Mn mines, foundries, smelters, and battery manufacturing facilities. In addition to neurological effects, adverse respiratory effects were reported in Mn-exposed occupational cohorts, including impaired pulmonary function, metal-fume fever, cough, and increased susceptibility to bronchitis and pneumonia (Lloyd Davies, 1946; Roels et al., 1987a, 1992; Antonini, 2003). In addition, a few studies reported adverse hematological, endocrine, or male reproductive effects following occupational exposure to Mn (Yiin et al., 1996; Alessio et al., 1989; Smargiassi & Mutti, 1999; Roels et al., 1987b, 1992; Lauwerys et al., 1985; Wu et al., 1996, as cited in ATSDR, 2000; Huang et al., 2001; Kim et al., 2007).

MANGANESE NEUROTOXICITY

Neurotoxicity in humans has been observed primarily in occupational settings where the potential exists for chronic inhalation exposure to high levels of Mn or following the accidental ingestion of large quantities of Mn. The brain is particularly susceptible to damage from high levels of Mn, and accumulation in this organ is associated with manganism, a neurodegenerative disorder characterized by both central nervous system (CNS) abnormalities and neurobehavioral disturbances.

Toxicological Studies

There have been few systematic attempts to study the effects of Mn on behavior using animal models, and most studies focus on neurochemical effects of Mn (McMillan, 1999; Newland, 1999). A critical first step in understanding the role that Mn plays in neurological disease is to determine exposure conditions that lead to increased concentrations of the metal within the CNS (Dorman

et al., 2002). This understanding is especially critical for Mn, because its mechanism of toxicity is poorly understood. It is known that brain delivery of Mn is higher in animal studies following inhalation versus ingestion, and that pharmacokinetic factors that may contribute to this increased efficiency in brain Mn delivery include increased absorption from the pulmonary tract, slower blood clearance of absorbed Mn, and direct delivery to the brain via the olfactory system (Andersen et al., 1999). Many experimental studies have been conducted to evaluate the fundamental issues of Mn toxicity, including the absorption and bioavailability of various chemical forms of Mn, mechanism(s) of toxicity, types of neurological effects, dose-response relationship, and the tissue distribution of Mn. Due to the complexity, expense, and difficulties encountered in inhalation experiments, most of the earlier data on Mn neurotoxicity were derived from studies where it was administered to rodents by routes other than inhalation, such as oral administration (Normandin et al., 2002), intraperitoneal injection (Chen et al., 2002), intranasal instillation (Tjälve and Henriksson, 1999), or intratracheal instillation (Vitrella et al., 2000). However, there have been rodent inhalation studies to evaluate the pharmacokinetics and/or the olfactory route for the transport of Mn to the brain (Wieczorek & Oberdörster, 1989; Brenneman et al. 2000; Vitarella et al., 2000; Yu et al., 2003; Normandin et al., 2002, 2004; Lewis et al., 2005; Dorman et al., 2001, 2002, 2004, 2005).

Most animal models are inadequate for evaluating the types of Mn-induced neurological effects observed in humans, making it difficult to study the mechanism(s) involved and elucidate a dose-response relationship for such effects. Most of the Mn inhalation toxicological studies have been conducted to evaluate the pharmacokinetics and bioaccumulation of Mn, not CNS changes. In addition, the types of neurological symptoms or brain pathology observed in humans have rarely been reported in rodents or primates treated with Mn (Normandin et al., 2002). Most experimental studies performed with rodents or primates have not detected CNS changes (e.g., behavioral, histological, biochemical), and the primary effects observed were transient alterations of spontaneous motor activity (Normandin et al., 2002).

One of the few studies that that reported neurological signs involved the administration of Mn oxide (MnO_2) subcutaneously to nonhuman primates for 5 mo, which resulted in dystonic[2] posture, unsteady gait, and an action tremor at the high exposure levels (Eriksson et al., 1987). Four nonhuman primates were exposed to a total of 8 g MnO_2 by repetitive subcutaneous injections during 5 mo, after which they were not treated for 1 wk to 6 mo before they were sacrificed. All animals developed hyperactive behavior after about 2 mo, and approximately 5 mo after the start of the exposure, the animals became hypoactive with an unsteady gait. An action tremor appeared subsequently in some of the animals, the animals lost power in both upper and lower limbs, and movements of the hands and feet were very clumsy. The serum content of Mn increased 10- to 40-fold above baseline during the exposure period, and the Mn content in brain tissue was generally more than 10-fold higher than normal, with the highest content found in the globus pallidus and putamen. The observed neurochemical effects were also greatest in these areas of the brain. Although the observations provide some information about Mn neurotoxicity, the dose was high, and the subcutaneous route of administration makes it difficult to extrapolate these results to humans. An early study was conducted to evaluate the effects of intraperitoneal injections of increasing doses of $MnCl_2$ (5–15 g every other day) in nonhuman primates for 18 mo (Mella 1924). All three animals developed abnormal movements and gait disturbances. Histopathological examination revealed changes in the liver and the striatum and pallidum of the brain. Another study involving intravenous injections of 10–14 mg/kg $MnCl_2$ in nonhuman primates every other week for 14 wk reported hypoactivity and abnormal extended posturing in the hind limbs in 2/3 animals (Shinotoh et al., 1995). Magnetic resonance images (MRIs) demonstrated high signal intensities in the striatum, globus pallidus, and substantia nigra. The authors concluded that the observation that the globus pallidus is the main target for Mn toxicity in nonhuman primates is consistent with findings in human patients with basal ganglia dysfunction due to Mn.

[2]Dystonia is a condition in which there is abnormal muscle tone, characterized by prolonged, repetitive muscle contractions that may cause twisting or jerking movements of the body or a body part.

Two subchronic inhalation studies of Mn in nonhuman primates were also conducted (Nishiyama et al., 1977; Ulrich et al., 1979a, 1979b). In one study, groups of 2 or 3 nonhuman primates were exposed to 0, 0.7, or 3 mg/m^3 per day respirable MnO_2 for 22 h/d, 7 d/wk, for 10 mo (Nishiyama et al., 1977). Two out of 3 nonhuman primates exhibited mild neurological signs (mild tremor of the fingers, loss of pinching force, loss in dexterity) following exposure to 3 mg/m^3 per d for 3–4 mo; however, the signs did not progress in severity during the 10 mo. Mn was measured in a variety of tissues and was found to have accumulated in the basal nuclei of the brain (caudate nucleus, pallidum, and putamen). Ulrich et al. (1979a, 1979b) treated groups of 8 nonhuman primates with respirable Mn_3O_4 at 0.012, 0.11, or 1.12 mg/m^3 for 24 h/d, 7 d/wk, for 9 mo. There were no effects on electromyograms or limb tremor in any of the exposed animals. Based on the results of Ulrich et al. (1979a, 1979b), a no-observed-adverse-effect level (NOAEL) of 5 mg Mn/m^3 was calculated by converting the data to an occupational exposure of 8 h/d, 5 d/wk (Clewell et al., 2003). Other more recent studies with nonhuman primates have been conducted to evaluate the pharmacokinetics and MRI changes following inhalation exposure to Mn (Dorman et al., 2006a, 2006b).

Animal studies may provide information about the absorption, bioavailability, and tissue distribution of various Mn compounds with different solubilities and oxidation states. In rats, increases in brain Mn delivery were observed with intranasal instillation or inhalation exposure following Mn absorption from the pulmonary tract and/or direct transport of Mn to the CNS along the olfactory or trigeminal nerve (Tjalve & Henriksson, 1999; Brenneman et al., 2000; Dorman et al., 2002; Lewis et al., 2005); however, the relevance of this route of Mn delivery to the brain in humans is not clear because of the many physiological differences in the olfactory system and the brain between rodents and humans (Aschner et al., 2005; Brenneman et al., 2000). Significant interspecies differences in nasal and brain anatomy and physiology exist (Aschner et al., 2005). Differences in the relative size of the rat olfactory mucosa and olfactory bulb likely predispose rats, more so than humans, to nasal deposition and potential olfactory transport of Mn; however, direct experimental evidence in support of this conclusion is lacking (Dorman et al., 2002; Aschner et al., 2005). Furthermore, the experimental animal inhalation studies that have been conducted to date are short-term, relative to the chronic exposures of occupational and nonoccupational populations (Aschner et al., 2005).

Other experimental studies evaluated the tissue distribution of different Mn compounds following absorption. For example, a few studies were conducted with rodents to evaluate the distribution of Mn in the brain following the inhalation of different Mn compounds (Dorman et al., 2001; Normandin et al., 2004). Dorman et al. (2001) reported that inhalation exposure to soluble Mn sulfate ($MnSO_4$) resulted in higher brain Mn concentrations than those resulting from exposure to insoluble Mn tetroxide (Mn_3O_4). A study conducted by Normandin et al. (2004) evaluated the absorption and distribution of Mn in the brain of rats following inhalation exposure to three chemical forms of Mn (metallic Mn, Mn phosphate/sulfate mixture, and Mn phosphate [Mn_5PO_4]). The authors found that the Mn concentrations in the brain were significantly higher in rats exposed to Mn phosphate and the Mn phosphate/sulfate mixture than in control rats or rats exposed to metallic Mn. They concluded that chemical species and solubility influence the brain distribution of Mn in rats. The results from such studies may provide useful information for understanding any differences in the rates of neurotoxicity reported in various occupational cohort studies that typically involve exposure to different Mn compounds and forms; however, questions regarding how much Mn can be absorbed and tissue distribution following inhalation exposure to various chemical forms in humans remain unanswered.

Mn Neurotoxicity in Humans

In humans, numerous neurobehavioral and neurophysiological effects were reported to be associated with Mn exposure, including both subclinical and clinical symptoms.[3] For several

[3]In this review, "subclinical" symptoms are those signs that are without clinical manifestations and may occur without progressing to the manifestation of overt clinical symptoms. Subclinical symptoms may also occur before symptoms become apparent or detectable by clinical examination or laboratory tests. "Clinical" symptoms are defined as signs or indications of disorder or disease that may be detected by physical examination or laboratory tests. They typically involve a change from normal function, sensation, or appearance in the subject.

Mn-exposed occupational groups, subclinical neurological symptoms such as decreased neurobehavioral performance (e.g., hand–eye coordination, response speed), decreased or impaired motor functions (e.g., hand steadiness, limb paresthesia, tremor), and neuropsychological effects (e.g., mood alterations, insomnia, and decreased memory) were reported (Gibbs et al., 1999; Iregren 1990; Huang et al., 1993; Lucchini et al., 1995, 1999; Mergler et al., 1994; Nelson et al., 1993; Roels et al., 1987a, 1992; Bowler et al., 2003, 2006a; Bast-Pettersen et al., 2004; Martin 2006; Lees-Haley et al., 2006; Park et al., 2006). In occupations with high levels of exposure, such as mining, smelters, and foundries, clinical neurological effects were associated with exposure to relatively high levels of airborne Mn. In some instances, the neurological effects included a collection of symptoms, such as muscle weakness and rigidity, distinctive altered gait, coordination and balance problems, mask-like face, neuropsychological disturbances, and loss of appetite. This collection of clinical neurological symptoms has been termed "manganism" and was found in several workers exposed to Mn, primarily prior to the 1970s when workers were likely chronically exposed to high airborne concentrations of Mn (Couper, 1837; Rodier, 1955; Schuler et al., 1957; Tanaka & Lieben, 1969; Whitlock et al., 1966; Mena et al., 1967; Smyth et al., 1973; Saric et al., 1977; Emara et al., 1971; Wang et al., 1989; Hua & Huang, 1991; Huang et al., 1998).

The neurological manifestations associated with Mn neurotoxicity are generally divided into three categories: (1) nonspecific neurobehavioral and neuropsychological changes, (2) subclinical neurological signs, and (3) clinical neurological and psychiatric manifestations of manganism (Mergler & Baldwin, 1997; McMillan, 1999; Pal et al., 1999). Subclinical, nonspecific neurofunctional changes may include a variety of subjective neurological or neurobehavioral symptoms, including anorexia, apathy, headaches, insomnia, muscle spasms, arthralgias (joint pain), irritability, and weakness. With increasing exposure to Mn, subclinical neurophysiological and neuromotor symptoms such as speech disorders and clumsiness in movements may manifest. Many studies evaluated subclinical symptoms associated with inhalation exposure to Mn, including decreased motor function, mood alterations, decreased hand steadiness, insomnia, decreased hand–eye coordination, increased tremor, decreased response speed, limb paresthesia, and decreased memory (Chandra et al., 1981; Roels et al., 1987a, 1992; Kondakis et al., 1989; Wennberg et al., 1991; Chia et al., 1993a, 1993b; Mergler et al., 1994; Hochberg et al., 1996; Sjögren et al., 1990, 1996; Lucchini et al., 1995; 1999; Luse et al., 2000; Sińczuk-Walczak et al., 2001; Iregren 1990; Park et al., 2006). There does not appear to be a general consensus regarding the most sensitive neurological endpoint for subclinical Mn toxicity, although Mergler and Baldwin (1997) reported that the motor tasks that appear to be the most sensitive to Mn exposure are those that require the participant to perform coordinated, sequential, alternating movements at maximum speed. Iregren (1994) also suggested that the ability to repeat simple movements might be particularly sensitive to Mn exposure and emphasized the need for investigations to study early signs of Mn toxicity through the use of behavioral methods in groups of active workers before the onset of clinically observable symptoms. However, many of the subclinical effects reported in the various Mn-exposed cohorts (1) have the potential for multiple etiologies and confounding variables (e.g., ergonomics, disease states, other exposures, age), (2) are self-reported and subjective, (3) often are not reproducible, and (4) are of uncertain functional and/or clinical significance (Clewell et al., 2003). The third category, clinical neurological and psychiatric manifestations of manganism, is characterized by persistent neurological deficits, such as muscular rigidity, gait disorder, tremor of the upper limbs, mask-like face, and other symptoms that may progress, possibly even in the absence of continued Mn exposure (Mergler, 1999; Normandin et al., 2004). Clinical neurotoxicity or manganism is the most significant toxicological consequence of Mn toxicity. In cases where Mn exposure levels were high or likely to be high, clinical neurotoxicity has often been reported as being irreversible even after the cessation of Mn exposure (Couper, 1837; Casamajor, 1913; Canavan et al., 1934; McNally, 1935; Fairhall & Neal, 1943; Rodier, 1955; Abdel Naby & Hassanein, 1965; Mena et al., 1967; Tanaka & Lieben, 1969; Greenhouse, 1971; Cook et al., 1974; Huang et al., 1993, 1998; Beuter et al., 2004).

There is some debate as to whether "progression" from subclinical to clinical effects can occur even in the absence of ongoing Mn exposure. Although Mergler et al. (1999) describe the manifestations of

Mn neurotoxicity as a continuum of dysfunction, a cross-sectional study of South African miners with a wide range of Mn exposure levels by Myers et al. (2003a) failed to document a continuum of effects (Martin, 2006). Overall, however, there is little evidence to suggest that individuals who exhibit subclinical neurological symptoms will progress and exhibit clinical symptoms (Crump & Rousseau, 1999). One 11-yr study found that individuals exhibiting subclinical neurological symptoms did not progress and exhibit clinical symptoms with continued occupational exposure to Mn (Crump & Rousseau, 1999). Even in some cases with clinical neurological symptoms, there is little evidence of progression following removal from exposure (Bleich et al., 1999; Cook et al., 1974; Lucchini et al., 1999). There is also evidence to suggest that some of the subclinical or less severe neurological effects are reversible once exposure ceases, particularly if the worker is removed from exposure promptly (Couper, 1837; Wilbur, 1932; Fairhall & Neal, 1943; Tanaka & Lieben, 1969; Smyth et al., 1973; Hine & Pasi, 1975; Roels et al., 1999). The issues of progression and reversibility of neurotoxicity warrant further study.

The neurological effects observed in Mn-exposed individuals are likely a function of duration and magnitude of exposure, absorbed dose, and individual susceptibility; however, the specific levels at which cumulative low exposure alters nervous system functions, and the dose-response relationship, remain unclear. Most of the studies that report clinical effects in individuals from various occupational settings involve Mn exposure levels that are higher than 5 mg/m^3, the current permissible exposure limit (PEL) for Mn (Mergler & Baldwin, 1997; American Conference of Governmental and Industrial Hygienists [ACGIH], 2001; Clewell et al., 2003). It is difficult to elucidate a dose-response relationship for Mn and subclinical neurological effects from the occupational cohort studies for a number of reasons, including: (1) The chemical or physical forms of Mn differ among the various industries (e.g., salts, dust, oxides, fume), (2) different exposure scenarios involve different activities, (3) reporting of different exposure measures (time-weighted average [TWA] vs. peak samples; area vs. personal; total dust vs. respirable), (4) lack of reported exposure levels, (5) differing neurological endpoints evaluated among studies, and (6) study design limitations (e.g., methodological flaws, selection bias, inappropriate case selection, lack of adequate control group). In addition, there is a possibility for a significant amount of intra-individual susceptibility to Mn due to age, preexisting diseases, gender, genetic factors, and the presence of other metals (e.g., iron and calcium) that compete for physiological receptor binding sites.

There does appear to be sufficient data to indicate that an exposure threshold exists for the subclinical neurological effects of Mn. For example, Gibbs et al. (1999) did not observe neurological effects in workers in a metal-producing plant exposed to levels averaging 0.18 mg/m^3 total Mn dust. A study by Deschamps et al. (2001) in enamel production workers exposed to Mn reported that chronic exposure (~20 yr) to approximately 0.2 mg/m^3 respirable Mn may induce potentially mild subjective symptoms (e.g., sleep disturbance, headache, weakness) but did not lead to adverse effects on nervous system function. In addition, studies by Myers et al. (2003a, 2003b) did not detect any subclinical or clinical neurological effects or deficits in two large cohorts of miners or smelter workers exposed to 0.21 mg Mn/m^3 (arithmetic mean). Thompson and Myers (2006) conducted a more in-depth statistical analysis of the neurobehavioral data from the Myers et al. (2003b) study. The association between neurobehavioral test scores and cumulative Mn exposure was estimated, and the investigators demonstrated that a linear model could be fit to these data with a statistically significant trend of an association between neurological effects and increasing exposure levels; however, the exposure-response relationship was highly nonlinear. Fitting a linear regression inappropriately to a nonlinear function can lead to misinterpretation of the results, and can obscure the existence of a threshold. This type of error is most likely to happen with small data sets that are frequently found in occupational epidemiology literature. Clewell et al. (2003) conducted a benchmark dose-response analysis of the Roels et al. (1987a) and Gibbs et al. (1999) studies in battery- and metal-producing workers. This study provides the best indication that a TWA occupational exposure limit between 0.1 and 0.3 mg/m^3 respirable Mn should be protective of subclinical neurological effects; however, additional analyses are clearly required to substantiate this proposition (Finley & Santamaria, 2005).

Manganism vs. Parkinson's Disease

Parkinson's disease (PD) and manganism can be differentiated based on the clinical, pharmacological, imaging, and pathological features of each condition (Olanow, 2004; Jankovic, 2005; Ostiguy et al., 2005). The distinguishing features between manganism and PD can be placed into the following categories: clinical, pathology, imaging, and response to treatment (Table 1). Similarities between the clinical manifestations of PD and manganism include, most notably, the presence of generalized bradykinesia (abnormal slowness of movement) and widespread muscle rigidity. The similarities between the two disorders may be explained partially by pathological features that have been observed, specifically the fact that the basal ganglia accumulate the most Mn compared with other brain regions in manganism, and dysfunction in the basal ganglia is also the etiology of PD (Dobson et al., 2004). Dissimilarities include less frequent resting tremor, more frequent dystonia, symmetry of effects, a particular propensity to fall backward, and a characteristic "cock-walk," in which manganism patients walk on their toes with elbows flexed and spine erect (Calne et al., 1994; Ostiguy et al., 2005; Jankovic, 2005). Further, PD is associated primarily with the loss of dopaminergic neurons within the substantia nigra, allowing the caudate and putamen to become overly active and possibly produce continuous output of excitatory signals to the corticospinal motor control system (Guyton & Hall, 1996). The substantia nigra is spared in manganism, which is linked to the degeneration of GABAminergic neurons within the globus pallidus in pathways postsynaptic to the nigrostriatal system (Pal et al., 1999; McMillan, 1999). The nigrostriatal pathway provides dopaminergic innervation to the caudate nucleus and the putamen, which is part of the system that modulates the flow of information from the cortex to the motor neurons of the spinal cord (McMillan, 1999). Another difference is the presence of Lewy bodies in the substantia nigra and other regions of the brain in PD but not in manganism (Olanow, 2004; Ostiguy et al., 2005).

There are also a few imaging procedures that have been used to distinguish manganism from PD, including positron emission tomography (PET), computerized tomography (CT), and magnetic resonance imaging (MRI). In patients with PD, the CTs and MRIs are typically normal and are not of diagnostic value, while the PET imaging of dopamine uptake sites is abnormal (Calne et al., 1994; Jankovic, 2005). PET provides a means of discriminating between PD and manganism, because the uptake of fluorodopa in the striatum of PD patients typically is reduced, due to the loss of dopaminergic cells in the nigrostriatal pathway (Calne et al., 1994; Olanow, 2004; Ostiguy et al., 2005). Manganism is generally associated with hyperintense signal abnormalities in the globus pallidus, striatum, and substantia nigra bilaterally on an MRI, whereas the MRI is normal in PD patients (Nelson et al., 1993; Olanow 2004). There are also differences with respect to treatment response. Although a patient may respond initially to L-dopa, the primary treatment option for PD, patients with manganism typically fail to achieve a sustained therapeutic response (Calne et al., 1994). Based on these criteria, it appears that it is possible to differentiate patients with manganism from patients with PD who may have had incidental exposure to Mn (Olanow, 2004; Ostiguy et al., 2005). Further studies of such patients are also likely to yield more factors that will assist in discriminating between PD and manganism.

TABLE 1. Diagnostic Features of Manganism versus Idiopathic Parkinson's disease

Disease	Clinical	Pathology	Imaging		Response to Treatment
			PET	MRI	
Manganism	Bradykinesia, rigidity, masked face, tremor, dystonia, falling backward, cock-gait walk	Neuronal loss in basal ganglia, primary target is globus pallidus, Lewy bodies rare	Normal	Abnormally high signal in globus pallidus, striatum, and substantia nigra	Initial response to levodopa, but not sustained
Idiopathic Parkinson's disease	Bradykinesia, rigidity, masked face, resting tremor, asymmetry, stooped gait	Neuronal loss, primary target is substantia nigra pars compacta, Lewy bodies observed	Reduced F-dopa uptake in posterior putamen	Normal	Sustained response to levodopa

HISTORY OF OCCUPATIONAL EXPOSURE LIMITS FOR MANGANESE AND WELDING FUME

Like many chemicals, no federal regulations or guidelines for Mn existed prior to 1950. The ACGIH set the only available occupational guideline for Mn in 1946, along with guidelines for several other chemicals. Initially, the term "maximum allowable concentration" (MAC) was used to describe the recommended exposure limit. In 1946, ACGIH set a MAC guideline of 6 mg Mn/m^3 as a time-weighted average (TWA) for total Mn (MAC-TWA), a value that remained in place until 1947. In 1948, the subcommittee changed the term to "threshold limit value" (TLV) after determining that the term MAC erroneously implied that the concentrations above the MAC posed a genuine potential health hazard (LaNier, 1984). Beginning in 1948, the ACGIH guideline was changed to a TLV-TWA. The TLV-TWA of 6 mg/m^3 for Mn was in place until 1959. Figures 1 and 2 show the Mn, Mn fume, and welding fume regulations promulgated by ACGIH, OSHA, and the National Institute for Occupational Safety and Health (NIOSH) over time, beginning in the 1940s to the present day. Both short-term (ceiling) and long-term (TWA) guidelines are shown. In particular, Figure 1 shows the regulatory timeline for elemental and total Mn, which includes Mn compounds and compounds of Mn present in inhalable dust. Figure 2 shows the regulatory timeline for both welding fume and Mn fume for both short-term and long-term guidelines.

The Public Health Service (PHS) also recommended nonbinding "permissible" concentrations of Mn in an occupational setting in the 1940s timeframe. In its National Institutes of Health Bulletin,

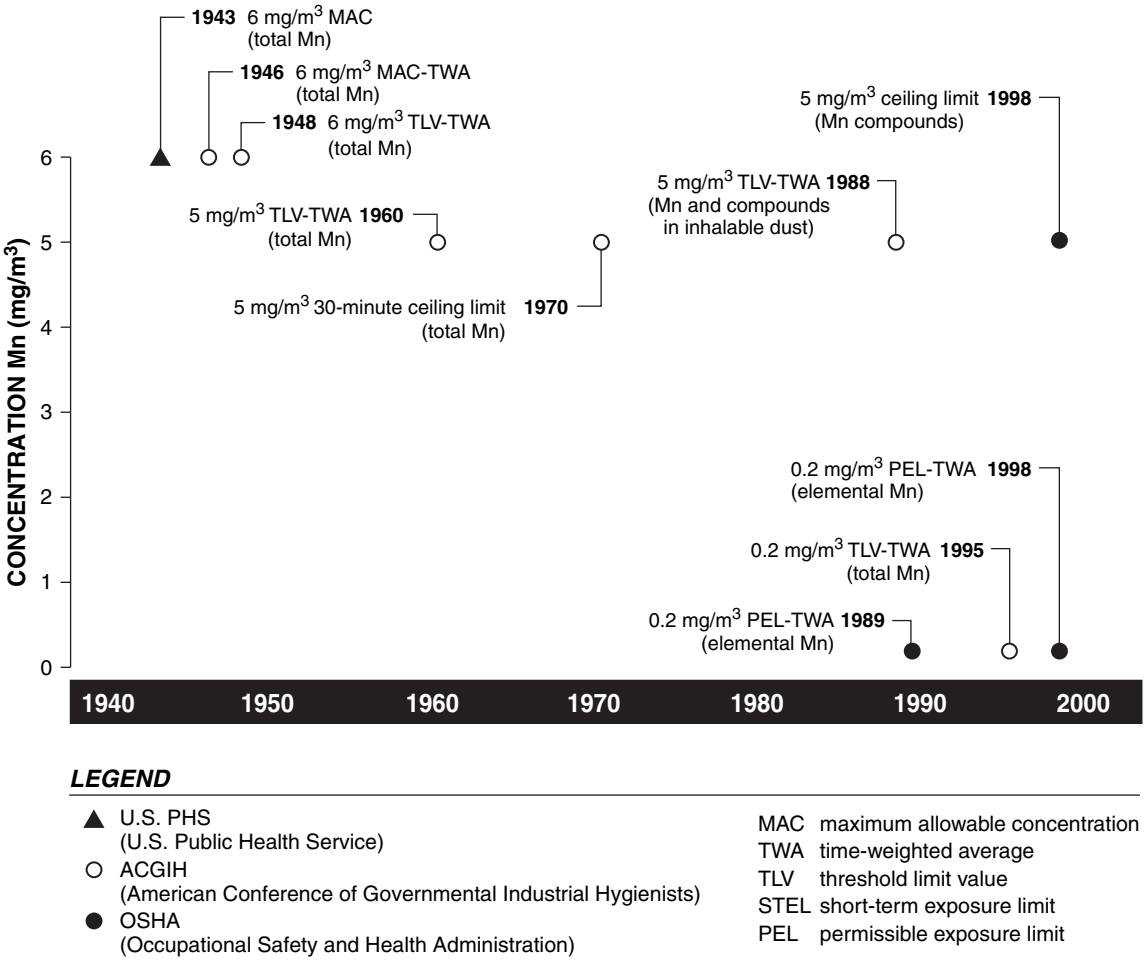

FIGURE 1. Chronology of occupational guidelines and regulations for total Mn and Mn compounds.

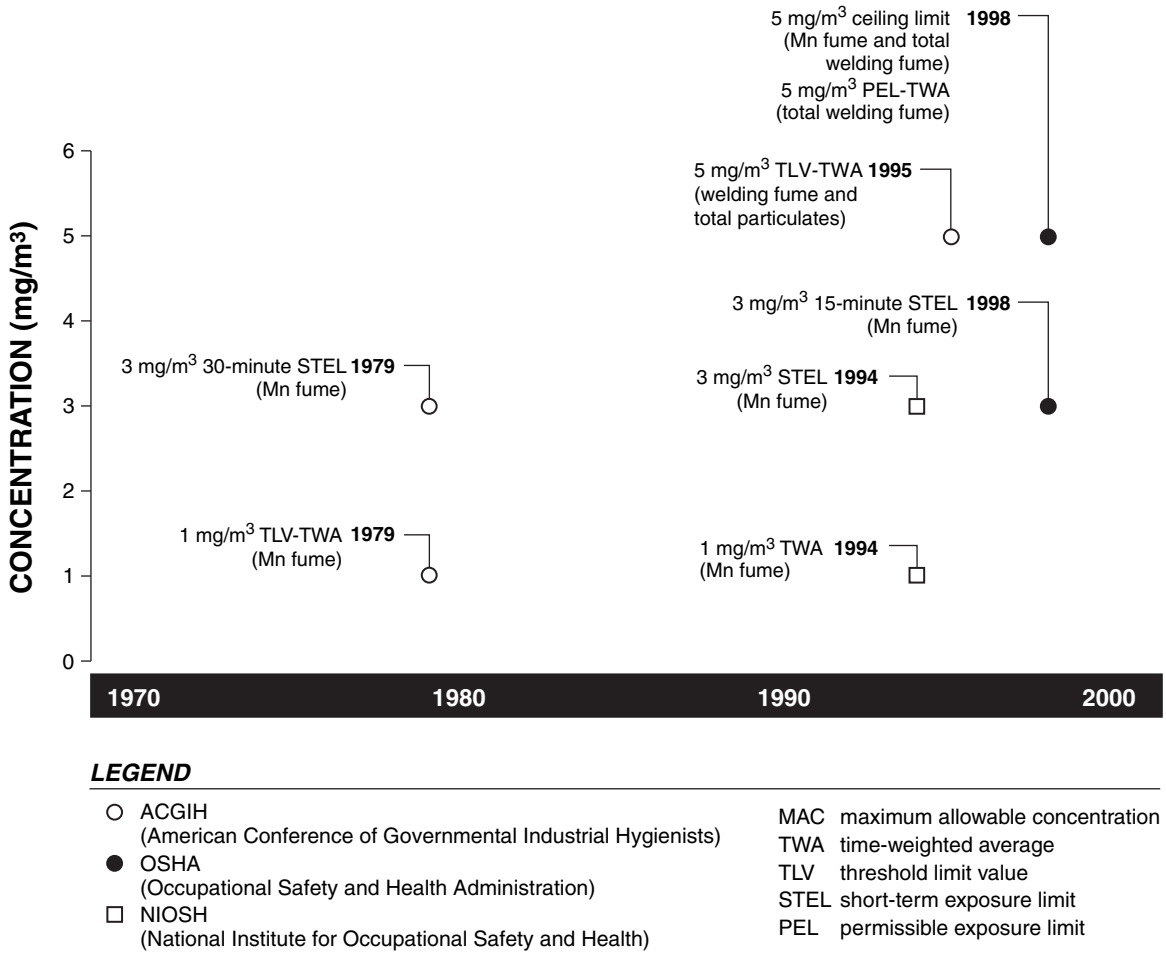

FIGURE 2. Chronology of occupational guidelines and regulations for Mn fume and welding fume.

the PHS described a study of workers in an ore-crushing mill (Flinn et al., 1940) where no cases of Mn toxicity were observed when exposures were in the range of 90 mg/m^3. The PHS stated, "The maximum permissible concentration of Mn has been tentatively placed at 60 mg per 10 m^3 of air" (Fairhall & Neal, 1943). A footnote to this sentence stated that this value was accepted and published by the American Standards Association in its American Allowable Concentration of Manganese document.

Federal Guidelines

With the establishment of OSHA, NIOSH, and other occupational health regulatory and research entities in the early 1970s, federal guidelines, occupational limits, and regulations went into effect during the latter years of this time period. Prior to this time period, the only available occupational guidelines for Mn were set by ACGIH, not federal agencies.[4] Occupational limits were

[4]The current TLV-TWA is intended to minimize adverse effects in the central nervous, respiratory, and male reproductive systems (ACGIH, 2001). The original TLV for welding fume (not Mn-specific) was 5 mg/m^3 for total particulates as a TWA and was reserved for metal arc or oxy-acetylene welding and cutting of aluminum, mild steel, and iron. ACGIH acknowledged that fumes from stainless steel and cadmium- or lead-coated steel, as well as base metals containing copper, nickel, and chromium, are appreciably more toxic, and as such, the governing criteria should be the substance-specific TLV. In 2003, ACGIH published a proposal to reduce the TLV-TWA for respirable Mn to 0.03 mg/m^3 (ACGIH, 2003). In 2004, ACGIH retracted the proposed TLV of 0.03 mg/m^3 for welding fume without giving an explanation for the retraction.

developed to protect workers from exposures to a variety of chemicals, including Mn fume, total particulates, and welding fume (Figures 1 and 2). The limits related to Mn were generally not based on neurotoxic endpoints, and were established to prescribe acceptable exposure limits in the occupational setting to prevent adverse respiratory effects. Several occupational guidelines and regulations existed for Mn and its various forms during this time period in different regulatory entities in both the United States and Europe. Many of these values were revised in the early to mid-1990s, as a result of new information regarding the neurological effects associated with Mn exposure in certain workers (Roels et al., 1987a, 1987b).

OSHA

In 1989, OSHA published various occupational limits for Mn (29 CFR [Code of Federal Regulations] 1910.1000, Table Z-1) (OSHA 1989b). These included a ceiling limit of 5 mg/m^3 for Mn fume and Mn compounds and a short-term exposure limit (15 min STEL) of 3 mg/m^3 for Mn fume. The studies upon which the ceiling limit of 5 mg/m^3 for Mn fume was based, as cited in the OSHA preamble, are relatively early studies for Mn toxicity that included symptoms such as walking difficulties and uncontrolled laughter, and studies evaluating the occurrence of pneumonia and bronchitis (Fairhall & Neal, 1943; Lloyd Davies, 1946; Tanaka & Lieben, 1969; Smyth et al., 1973; Stokinger, 1981). Based on results presented by ACGIH, OSHA also proposed a PEL-TWA of 0.2 mg/m^3 for elemental Mn and its organic compounds. In the preamble of the OSHA 1989 documentation (54 FR 2332; 54 FR 14909; 54 FR 28154) (OSHA 1989a), the current limit for Mn fume PEL is based on neuropathy or avoidance of neuropathic effects. At the time, OSHA also promulgated a PEL-TWA of 5 mg/m^3, which originally was a ceiling value for total welding fume in general industry and as a TWA for the construction industry. Welding fume, as defined by OSHA, contains metallic oxides generated by the heating of the metal being welded, the welding rod, or coatings on either the parent metal or the consumable rod. The original OSHA PEL for welding fume was eventually rescinded. No current PEL for welding fume exists, but OSHA promulgated standards for specific metals and gases that may be generated by welding, brazing, and thermal cutting activities.

NIOSH

Due to the presence of chromium and nickel in some welding fumes, NIOSH considers welding fumes to be carcinogenic and established a recommended exposure limit (REL) for welding fumes (and total particulates) of the lowest feasible concentration (NIOSH, 2004). Because of the complex chemical composition and structure of welding fume, NIOSH suggested that it is not feasible to establish an exposure limit for total welding emissions, and exposure limits may be needed for each welding fume constituent. NIOSH established other RELs for specific elements and gases that may be present in welding fume emissions, depending on the welding rods, base metals, and surface treatments used. In addition, NIOSH set two RELs for Mn fume—a TWA of 1 mg/m^3 and an STEL of 3 mg/m^3.

GENERAL BACKGROUND ON WELDING ACTIVITIES

A total of 452,000 workers were employed as welders, cutters, solderers, and brazers[5] in the United States in 2002 (Bureau of Labor Statistics, 2005), and there are more than 2 million workers who perform some type of welding as part of their work duties (Antonini et al., 2006). In industrialized countries, 1–2% of the work force is engaged in welding (Stern et al., 1986; Voitkevich, 1995; Hewitt, 2001). Their exposure to metals varies greatly according to the metal being welded, the type of electrode being used, and coatings that may be on the material being welded (Stern et al., 1986; Burgess, 1991; Antonini, 2003). In addition, the specific welding process and work environment

[5]Soldering and brazing refers to metal-joining techniques where solder (usually tin–lead or copper–zinc alloys) and nonferrous metals are used to unite metals, respectively. For purposes of this article, brazers and solderers are considered in the analysis of welders, because the American Welding Society identifies this method as a welding process. Brazing involves use of a molten filler material that is introduced between two metals to form a bond when heated above 800°F (Beckett, 1996).

(e.g., quality of ventilation; outdoors versus confined space) may also affect exposure (Burgess, 1995; Beckett, 1996). More than a dozen welding techniques are commonly encountered in the industry (Burgess, 1991), although the American Welding Society (AWS) has identified more than 80 different types of welding and allied processes in commercial use (Villaume et al., 1979; Burgess, 1995).

The four most common welding techniques are gas tungsten arc/tungsten inert gas welding (GTAW or TIG), gas metal arc welding/metal inert gas welding (GMAW or MIG), flux-cored arc welding (FCAW), and shielded manual metal arc welding (MMAW or SMAW)[6] (Stern et al., 1986; Hemminki et al., 1985; Burgess, 1991; Kura & Mookoni, 1998; Antonini et al., 2006). These 4 techniques make up 80–90% of all manufacturing and maintenance welding, and are used by over 500,000 welders and helpers in the United States (Burgess, 1991). Most welding is performed on unalloyed steel, or so-called mild steel (Burgess, 1991). The composition and quantity of the welding fumes and gases generated vary with the welding materials and process. Generally, the consumable contributes 80–95% of the fume, because it is partially volatilized during the welding process (Stern et al., 1986; Antonini, 2003); vaporization of the parent metal accounts for less than 10% of the total welding fume (Kura & Mookoni, 1998). Other contributors to the content of the fume include the metals being welded, gaseous fume generated during the welding process, paint or surface coatings present on metals and/or electrode, inert shielding gases, fluxes, impurities of the metal, and atmospheric pollution (Antonini, 2003). The rate at which fume is generated depends on the welding process itself (e.g., welding current/voltage, arc length, type of shielding gas), composition of the consumable, geometry of the weld and of the consumable, and the skill level of the welder (Villaume et al., 1979; Stern et al., 1986; Voitkevich, 1995; Antonini, 2003).

Elements commonly present in welding fumes include aluminum, arsenic, calcium, chromium, copper, fluorine, iron, lead, magnesium, Mn, nickel, silicon, sulfur, titanium, vanadium, and zinc (NIOSH, 1988; Burgess, 1991; American Welding Society and Safety Committee [AWSSHC], 1993; Smyrloglou, 1993) (Table 2). The primary component of fumes generated from most welding processes is iron oxide as Fe_3O_4 (Burgess, 1991, 1995). The type of metal present in the fume depends on physicochemical properties of the metal itself (e.g., vapor pressure, boiling point), welding temperature, type of welding material, and concentration of metal in the electrode or welding material (Burgess, 1991). For example, stainless steel electrodes may contain approximately 20% chromium and 10% nickel, whereas fumes from mild steel welding are usually >80% iron with some Mn and no nickel or chromium (Antonini, 2003). Most welders are continuously exposed to airborne concentrations of iron that are considerably higher than that of Mn (Antonini et al., 2006). Korczynski (2000) evaluated personal exposures to welding fumes in 42 welders and reported that 19% of welders were exposed to levels of iron that exceeded the TLV-TWA of 5 mg/m^3 and the personal exposures ranged from 0.04 to 16.3 mg/m^3. The personal exposures to Mn ranged from 0.01 to 4.93 mg/m^3, and 62% of the welders were exposed to levels exceeding the TLV-TWA of 0.2 mg/m^3.

Mn is found in most mild steels, and is often used in steel alloys to improve metallurgical properties, providing both strength and hardness (Burgess, 1991; Barceloux, 1999). This metal is an essential ingredient of steel, serving to neutralize the effects of sulfur, enable forging and rolling processes, and enhance strength, toughness, and hardness. Introduction of Mn also provides deoxidizing reactions, and aids in minimizing weld impurities (Voitkevich, 1995). Mn oxides are used as flux agents in the coatings of shielded metal arc electrodes, in the flux-cored arc electrodes, and as an alloying element used in electrodes (Villaume et al., 1979). Mn is also often added to consumables, with electrodes containing between 2 and 15% Mn (AWS, 1979). In welding fume, Mn generally constitutes 0.2 –10% (AWS, 1979; Arnold, 1983; Burgess, 1995), and is likely present as "spinels" (e.g., [Fe, Mn]O Fe_2O_3 or $MnO{\bullet}MnFe_2O_4$) or mixed metal oxides such as MnO_2 and Mn_3O_4

[6]Other welding techniques discussed in the literature are gas welding and plasma arc welding. As the name implies, gases are used to obtain the heat of fusion in gas welding. Specifically, combustion of oxygen and several gases (including acetylene, methylacetylene, propadiene, propane, butane, and hydrogen) creates a flame that melts the work piece. A hand-held torch is used as a flame, while a metal rod is manually fed into the joint to create the weld (Kura & Mookoni, 1998). For plasma arc welding, an ionized stream of gas (plasma) carries the arc through a torch (Kura & Mookoni, 1998).

TABLE 2. Common By-Products Found During Welding Operations

By-Product	Source
Metal fume	
Aluminum	Metal additives, coatings and paints, filler wire
Cadmium	Plating, fluxes
Chromium	Stainless steel, electrode, plating, chrome-primed metal
Copper	Coating on filler wire, electrode sheaths, non-ferrous alloys
Fluorides	Electrode coverings (flux, slag)
Iron	Parent iron or steel metal, electrode, mild steel
Lead	Lead paint, electrode coating
Manganese	Welding rod, alloys in steel, flux coating, alloy in electrodes
Magnesium	Welding rod, alloys in steel
Molybdenum	Welding rod, alloys in steel
Nickel	Stainless steel, nickel-clad steel, nickel alloys
Silica	Flux, electrode coating
Tin	Tin-coated steel
Vanadium	Welding rod, alloys in steel
Zinc	Galvanized or zinc-primed steel, galvanized coatings
Fluorides	Flux on electrode
Gases and Vapors	
Carbon dioxide	Coatings and cores; shielding gas
Carbon monoxide	Coatings and cores; shielding gas
Nitrogen oxide	All flame processes
Nitrogen dioxide	All flame processes
Ozone	Photochemical reaction (O_2 and ultraviolet light)

Information obtained from Burgess 1991, Sferlazza and Beckett 1991, Antonini 2003.

(Lucchini et al., 1995; ATSDR, 2000; Hudson et al., 2001), with the most probable oxidation state of Mn being the divalent state (Voitkevich, 1995).[7] Some special steels containing high concentrations of Mn may produce relatively high concentrations of MnO_2 in welding fume (Moreton, 1977).

STATE-OF-THE-SCIENCE REVIEW

The state-of-the-science review is divided into three time periods: pre-1950, 1950 through 1980, and post-1980. The first period covers the initial case reports that suggested that exposure to high concentrations of Mn dust might produce adverse clinical neurological effects. The second time period, 1950 to 1980, is defined by an increasing number of epidemiological studies of workers with relatively high Mn exposures, such as miners, millers, battery workers, and chemical plant workers. The most relevant and thorough studies are discussed in this review, while others are mentioned briefly due to lack of detail provided in the original study regarding methodology or interpretation of results. The third period, post-1980, is marked by an increasing number of studies that focus on neurological effects in welders.

Pre-1950: Case Reports

Dr. John Couper of Scotland first described Mn toxicity in the medical literature in 1837. Couper reported adverse neurological effects, including muscle weakness, a staggering gait, whispering speech, salivation, and mask-like face, in five men who were grinding Mn in a chemical plant that manufactured chlorine for bleaching powder. Couper did not report any tremors in any

[7]Studies attempting to determine the chemical form of manganese, as well as its location within a welding particle, are lacking. Due to its vapor pressure, manganese tends to be found within the particle core when mild steel welding alloys are used (Voitkevich 1995). When welding alloys contain fluorine (e.g., when welding with flux-cored or flux-coated alloys), manganese can also be found at the particle surface in the form of MnF_2 or MnF_3 (Voitkevich 1995). Other possible forms of manganese observed in welding fumes include $MnFe_2O_4$, MnF_2, $MnSiO_3$, $KMnO_2$, $KMnF_3$, MnO, K_2MnO_4, Mn_3O_4, γ-Mn_2O_3, MnO, and $MnFe_2O_4$.

part of the body, nor did he observe any changes in cognition or sensory abilities. He described the workers as "grinding the black oxide of manganese. . . . The surface of their bodies is of course constantly covered with the manganese; the air which they breathe is loaded with it in the form of fine powder, and they are ever exposed, from neglect of cleanliness, to swallow portions of it along with their food." In two of the cases where symptoms were observed over a significant period of time, there was little or no lessening of the symptoms once the workers were removed from exposure. In three other cases, where workers were removed from their jobs as soon as symptoms were noted, complete recovery was attained in only a few weeks (Couper, 1837).

In the first half of the 20th century, cases of Mn-induced neurotoxicity were described in the scientific literature throughout the world (Embden, 1901; von Jaksch, 1901, 1907; Grewel & Sassen, 1939; Ansola et al., 1944 [all as cited in Fairhall & Neal, 1943, or Mena, 1979]; Casamajor, 1913; Edsall et al., 1919; Davis & Huey, 1921; Wilson, 1922; Kober, 1924; Gayle, 1925; Charles, 1922, 1927; Wilbur, 1932; Canavan et al., 1934; Owen & Cohen, 1934; McNally, 1935; Nazif, 1936; Scander & Sallam, 1936; Bryan, 1937; McCormick, 1937; Wilkinson, 1940; Flinn et al., 1940). Mn exposure as little as 3 mo prior to the development of neurological symptoms was described, although most case reports involved more typical exposures of 1 to 4 yr in occupations handling raw Mn. Few studies reported Mn exposure concentrations, although some, such as Davis and Huey (1921) and Wilkinson (1940), reported Mn concentrations in dust and fume as 38–72% and 19%, respectively. Some studies evaluated Mn concentrations in blood, urine, feces, skin, and cerebrospinal fluid (Charles, 1922; McCormick, 1937; Bryan, 1937; Wilkinson, 1940). Prior to 1950, a few studies reported autopsy findings in which neuropathological changes in the brain were observed in Mn-exposed workers (Casamajor, 1913; Ashizawa, 1927, as cited in Canavan et al., 1934; Trendtel, 1936, as cited in Abdel-Naby & Hassanein, 1965). By 1943, the PHS estimated that 350 case reports of neurotoxicity associated with exposure to Mn had been described in the literature subsequent to Couper's initial report (Fairhall & Neal, 1943). In 1935, McNally noted 131 such cases; however, case reports are merely clinical observations and are not epidemiological studies, which are more useful for evaluating whether a causal association may exist between exposure to a substance such as Mn and adverse health effects. Despite the number of cases reported, the PHS stated, "It would appear that industrial Mn poisoning is relatively a rarity considering the manifold technical applications of its compounds" (Fairhall & Neal, 1943).

In the early 1900s, von Jaksch first described the characteristic "cock walk" sometimes seen in Mn neurotoxicity, although the most likely diagnosis was thought to be an atypical instance of multiple sclerosis (von Jaksch, 1901, as cited in Fairhall & Neal, 1943). In 1913, Casamajor described 9 cases of neurotoxicity among workers in a separating mill connected to a large ore mine in the United States. The duration of employment at the mill ranged from 6 mo to 3 yr, and symptoms included gait disturbances, such as difficulty walking downhill or backward; mask-like face; asynergia (poor coordination); tremors of the tongue; and a fine static tremor of the hands. There was no muscle weakness or changes in reflexes, and no definitive signs of mental deterioration reported in the cases. Although 85 different ores were found at the mine, the author concluded that Mn was the most likely cause of the neurological symptoms; however, no information on exposure levels was provided in the study (Casamajor, 1913).

In 1919, Edsall et al. described a set of symptoms that they believed provided a "strikingly definite diagnosis of chronic Mn poisoning" based on their review of existing literature and examinations of 38 symptomatic mill workers in the United States. The symptoms included a history of at least 3 mo of exposure to Mn dust (levels not stated), sleepiness, fatigue, mask-like face, low monotonous voice, twitching or tremors, cramps and leg stiffness, slight increase in tendon reflexes, ankle and patellar clonus,[8] a distinctive gait disturbance, and sometimes uncontrollable laughter or crying. The authors observed that the shortest exposure duration prior to observable symptoms was about 6 wk, and the shortest duration associated with irreversible symptoms was 4 mo. Given the

[8]Patellar clonus refers to a rhythmic jerking movement of the patella produced by grasping it between the thumb and forefinger and pushing it suddenly and forcibly toward the foot. This is an abnormal reflex with alternate contraction and relaxation of the quadriceps muscle.

widespread and varied uses of Mn, along with the relatively few cases of observed Mn toxicity, they concluded that Mn was only slightly toxic and that only a small number of individuals were susceptible. Their recommendations for protecting workers' health emphasized early detection, dust control, and prompt removal of any symptomatic worker from continued exposure to Mn dust. Subsequent to the Edsall et al. (1919) study, reports from many countries described Mn toxicity in ore mills and foundries, and in the late 1930s and 1940s, manganism began to be reported in miners in Morocco, Africa, Chile, and Germany (Rodier & Rodier, 1949; Buttner & Lenz, 1937; Ansola et al., 1944, all as cited in Mena, 1979; Nazif, 1936). In 1932, a German study described two cases of Mn toxicity in electro-welders exposed to Mn-containing electrodes (Belniker, 1932, as cited in Fairhall & Neal, 1943). Lloyd Davies and Harding (1949) also reported an increased incidence of pneumonitis associated with inhalation of potassium permanganate and Mn dust (41–66% MnO_2), although frank signs of neurotoxicity (or systemic toxicity) were not observed and no overt cases of Mn poisoning were seen after 9 yr of observation.

In 1947, the PHS evaluated the respiratory health of arc welders in steel ship construction as a result of complaints of "shipyard cough," "welder's wheeze," and "welder's bronchitis" (Dreessen et al., 1947).[9] In addition to the PHS, several investigators, including the Division of Shipyard Labor Relations, U.S. Maritime Commission, and U.S. Navy Department, conducted this study of 4,650 workers in 7 Navy-contract shipyards in 1944. About 3 of every 4 persons examined was an oxy-acetylene welder, totaling 3,234 welders, and worked in the inner bottoms and other confined spaces of vessels under construction. Particular attention was focused on past occupations such as mining, sand blasting, quarry work, stone crushing, painting, and lead burning, to assess other occupational exposures. Dreessen et al. (1947) focused primarily on respiratory health effects of welders and others involved in shipyard work. Although metal fume fever is discussed in this study, it was limited to pipe welders working on galvanized pipe and exposed to zinc, and was described as "transient and apparently benign in nature," Dreessen et al. (1947) note that concentrations of Mn, aluminum, and magnesium were "in concentrations too low to give rise to the symptom complex [of metal fume fever]." It should be noted that the medical record form did assess nervous symptomology, including vertigo, paresthesia, insomnia, and irritability,[10] but these symptoms, if reported, were not discussed. Samples of fume and gas were taken during welding operations in the welders' breathing zone (i.e., sampler over the welders' shoulders), as well as general air samples, and analyzed for iron, total fume concentration, zinc, lead, and oxides of nitrogen (total of 1,900 samples). Samples were not evaluated for Mn concentration, although other studies are cited as finding 2–12% Mn in welding fume derived from welding mild steel; however, samples were taken of various electrode coatings, showing Mn contents of <5–20% ferrous Mn. Mn was also found to be present at concentrations of 0.4–0.6% in mild steel and 0.4–2.5% in stainless steel. Mean concentrations for total fume ranged from 31.1 to 87.5 mg/m^3; however, "Of the total fume samples taken in the hull, 14.2 percent exceed 100 mg/m^3, while of those from the subassembly and from the shop, 9.4 percent and 6.4 percent, respectively, exceed 100 mg/m^3." The study concluded, "In general, the concentrations of welding fume and gas observed in the environment phase of the study were relatively low, and the clinical findings were minimal" (Dreessen et al., 1947).

1950–1980: Focus on Miners, Millers, Plant, and Battery Workers

By 1960, more than 400 cases of individuals with neurological symptoms attributed to Mn exposure were reported (Tepper, 1961; Mena, 1979). The Mn exposures for the described cases varied from as little as 3 mo to several years prior to the onset of symptoms (Tepper, 1961), with

[9]The PHS also conducted a study in 1940 of workers in an ore-crushing mill exhibiting symptoms of extrapyramidal involvement of the CNS and pronounced changes in speech and gait (Flinn et al., 1940). A health survey of 50 workers, 11 of whom were exposed and "affected" and 23 classified as "exposed/not affected," showed no cases of Mn poisoning in workers exposed to <30 mg/m^3 of Mn; however, the authors note that the small sample size and intermittent exposure experienced by the workers suggest further research was required, recommending that quarterly medical exams be conducted, ventilation continue to be used, and workers exhibiting symptom be transferred from areas with possible Mn exposures.

[10]The "symptomatology" section of the medical record form states, "NERV.: Vert. ….. Parest. …. Insom. …. Irritab. …." These are presumed to be nervous symptomology, including vertigo (vert), paresthesia (parest), insomnia (insom), and irritability (irritab).

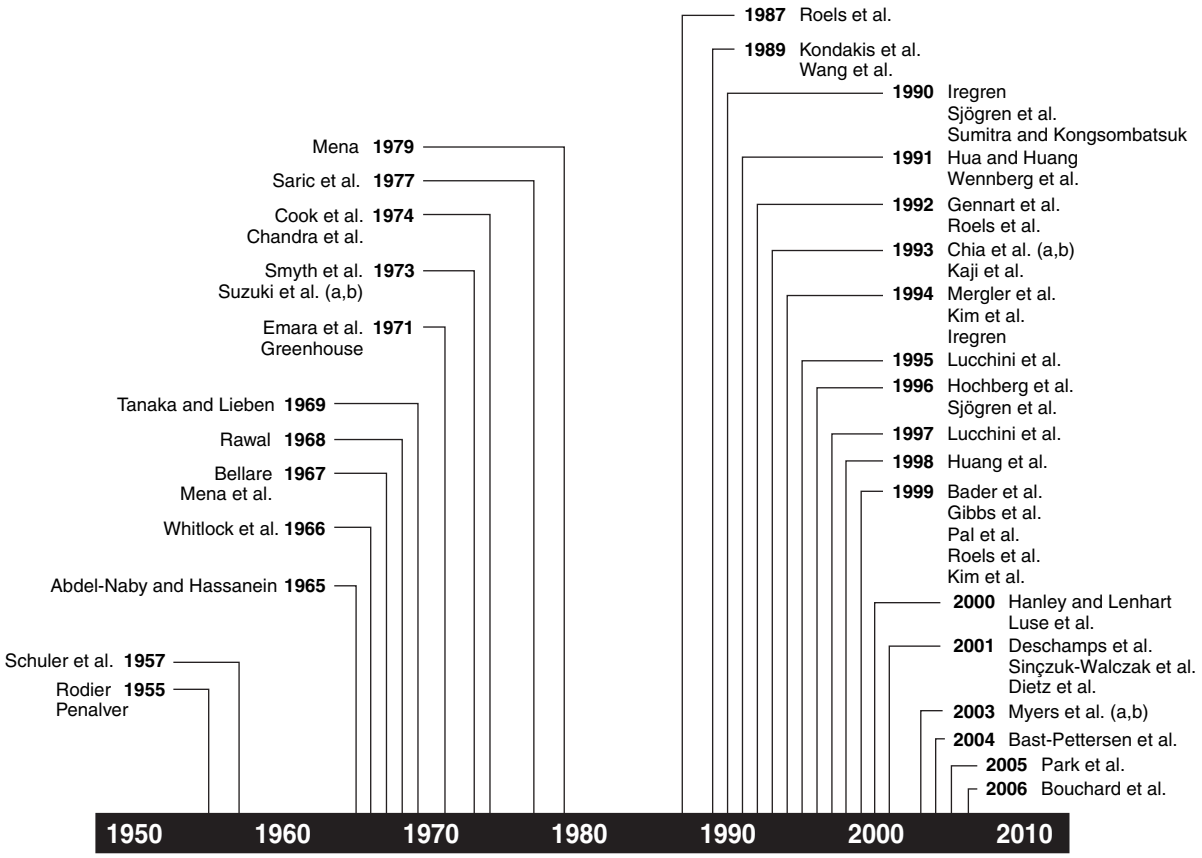

FIGURE 3. Timeline of studies evaluating neurological endpoints in non-welder occupational cohorts exposed to manganese.

concentrations reported to be higher than contemporaneous workplace guidelines in the 1960s. As shown in Figure 3, during this time period, several investigators began to evaluate occupational cohorts with high Mn exposures, such as miners (Rodier, 1955; Schuler et al., 1957; Abdel-Naby & Hassanein, 1965; Bellare, 1967 as cited in Mena, 1979; Rawal, 1968; Chandra et al., 1974), battery workers[11] (Emara et al., 1971), crushers or processors in ore mills (Greenhouse 1971; Cook et al., 1974), and assorted plant workers, including those working with ferromanganese alloys (Tanaka & Lieben, 1969; Smyth et al., 1973; Suzuki et al., 1973a, 1973b) and steel (Whitlock et al., 1966; Tanaka & Lieben, 1969). As described in more detail later in this article, many of these studies reported a high prevalence of symptoms such as headache, anorexia, memory loss, and excessive fatigue in those with the highest Mn exposures (Tanaka & Lieben, 1969; Smyth et al., 1973). These early symptoms were generally subjective in nature or related to psychological disorders. Reports of tremors, muscular rigidity, difficulty with balance, and spasms with "weakness of the legs" were also noted (Penalver, 1955). With extended periods of exposure, an increase in the frequency of neurological symptoms and extrapyramidal signs (e.g., tremors, rigidity, temporary paralysis, and extreme slowness of movement) was observed. These often included extreme psychomotor excitement, termed "manganese madness," which encompassed nervousness, irritability, aggression, and uncontrollable laughing or crying (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967). A few studies of welders began to appear, but most of the studies during this time period focus on mine workers or those millers involved with crushing or other processing of the ore

[11]Dry battery powder consists of 65–70% manganese as MnO_2, which serves as a depolarizing agent. Other components of dry battery powder include ammonium chloride, zinc oxide, graphite, acetylene black, ammonium hydroxide, cerium-thorium nitrate, magnesium nitrate, and mercuric chloride (Emara et al., 1971).

itself, where handling the raw material in a dusty environment likely resulted in the highest exposures (Pal et al., 1999). In general, fewer cases of neurotoxicity were described in battery workers than in miners and millers (Tepper, 1961). However, it is difficult to ascertain the incidence of neurotoxicity in any of these cohorts because the pool of workers for occupations such as mining was frequently changing (Rodier, 1955), and the bulk of published literature focused on workers with symptoms, without including any information on nonaffected workers, which would be necessary to develop estimates of incidence.

As in the mining industry, exposure levels of Mn experienced by plant workers in the metal industries were also comparatively high, and with the advent of occupational guidelines became of greater concern to scientists, regulators, and the general public. Overt manganism was reported at exposure levels as low as 2 mg Mn/m^3 to approximately 20 mg Mn/m^3 in studies of a variety of workers exposed for different periods of time, but no dose-response relationships were established (Rodier, 1955; Schuler et al., 1957; Whitlock et al., 1966; Tanaka & Lieben, 1969; Cook et al., 1974; Saric et al., 1977). Although the installation of ventilation helped reduce the overall exposure (Whitlock et al., 1966; Smyth et al., 1973), there was little description of such systems. Some authors stated that the TLV during this time period (which was 6 mg/m^3 in the 1950s and 5 mg/m^3 in the 1960s through 1978) was not protective of workers and suggested that it be lowered.

Beginning in the 1960s, studies focusing on neurological signs and symptoms among Mn-exposed workers reported a high prevalence of symptoms such as headache, anorexia, memory loss, and excessive fatigue in those with the highest Mn exposures (Tanaka & Lieben, 1969; Smyth et al., 1973). These symptoms were generally subjective in nature or related to psychological disorders. Reports of tremors, muscular rigidity, difficulty with balance, and spasms with "weakness of the legs" were also noted (Penalver, 1955). With extended periods of exposure, an increase in the frequency of neurological symptoms and extrapyramidal signs (e.g., tremors, rigidity, temporary paralysis, and extreme slowness of movement) were observed. These often included extreme psychomotor excitement, termed "manganese madness," which encompassed nervousness, irritability, aggression, and uncontrollable laughing or crying (Rodier, 1955; Schuler et al., 1957; Mena et al., 1967).

In 1957, Penalver suggested the use of chelating agents such as dimercaprol (BAL), edetic acid, and calcium ethylenediamine tetraacetic acid (CaEDTA) to remove excessive Mn in individuals exhibiting neurotoxicity (Mena, 1979). While Cotzias and coworkers (1967) were the first to utilize levodopa (L-dopa) as a form of treatment for manganese poisoning,[12] other investigators continued to question the efficacy of this treatment. Controversy still existed as to whether removal from the exposure source would halt the progression of symptoms of Mn toxicity, and some investigators attempted to evaluate the efficacy of various chemical treatments to stop, and potentially reverse, the symptoms. The rationale for the use of L-dopa developed from several studies showing that dopamine, which normally occurs at high concentrations in the basal ganglia and substantia nigra, was markedly depleted in the autopsied brains of persons who had PD (e.g., Hornykiewicz, 1963, as cited in Mena, 1979; Hornykiewicz, 1966). Although dopamine was proven to be ineffective due to its inability to cross the blood–brain barrier, dopamine's metabolic precursor, L-dopa, does cross this barrier and is presumably converted to dopamine in the basal ganglia (Cotzias et al., 1967). The use of L-dopa in the case of Mn-associated symptoms would relate to the role of dopamine in the symptoms or damage observed with exposure to high levels of Mn. L-dopa works in PD because the motor symptoms are due to a loss of dopamine in the caudate putamen and L-dopa treatment results in an increase in dopamine in that area, with a lessening of the motor movement problems. Although Mn is considered to impact basal ganglia, it does not produce severe loss of dopamine in the caudate putamen. However, because the symptoms of Mn toxicity involved motor problems, and there was little information on the neurochemical aspects of Mn, it made sense to try L-dopa treatment.

[12]Carlsson et al. (1957, 1958) were the first to discover that dopa, the inactive precursor to dopamine, was converted to dopamine in vivo in animal brains and could be used as a neurohumoral agent; however, it was not until 1967 that Cotzias discovered a mode of administration wherein the L-dopa was successfully incorporated into the CNS (Mena, 1979), and "marked improvement" was observed in 8 of 16 patients with PD treated with oral L-dopa (Cozias et al., 1967).

Studies of Exposure and Health Effects During this time period, many of the published studies focused on mine workers and millers working with raw materials, although evaluations of factory workers, such as foundry workers or those in smelters and alloy processing facilities, and others, were also conducted. Most of these studies typically examined either health effects or exposure levels; few studies attempted to correlate health effects with exposure levels. Two of the more comprehensive studies conducted during this time period that evaluated the correlation between health effects in plant workers and exposure levels were those of Tanaka and Lieben (1969) and Smyth et al. (1973). Tanaka and Lieben evaluated 75 Pennsylvania plants involved in various Mn industries, studying neurological symptoms, exposure levels, and biological indices of exposure. Smyth et al. (1973) evaluated employees of a single Pennsylvania ferromanganese processing and production plant. This study encompassed three phases of investigation, including the nature of exposure, epidemiology, and study of health effects. Both of these studies provide the most relevant information in this time period for associating Mn exposure with neurological symptoms (both studies are described in more detail in the later section entitled "Plant and Factory Workers").

Miners and Millers Several studies of miners and ore millers were conducted during this era, covering many geographic areas (Rodier, 1955; Schuler et al., 1957; Abdel-Naby & Hassanein, 1965; Greenhouse, 1971; Chandra et al., 1974; Cook et al., 1974). Several of these investigators observed neurotoxicity in three degrees of severity—mild, intermediate, and severe—but could not link physical symptoms to exposure levels. These studies generally reported the estimated exposure concentrations and/or duration and symptomology of workers exhibiting manganism, but did not describe exposure variables for nonsymptomatic workers. One study indicated mean exposure periods for these workers of 8 or 9 yr (Rodier, 1955), although the onset of symptoms typically occurred after 1 or 2 yr of exposure, with some occurring as early as 1 mo or as late as 25 yr. The workers with the highest exposures, primarily drillers of dry ore, appeared to be the group most affected and symptomatic. For example, Rodier (1955) evaluated a manganese mine in Morocco, noting 150 cases of manganism in underground drillers or persons working near the drillers. The miners were exposed to Mn concentrations ranging from 65 to 926 mg/m^3 during work with rock ore, powdery ore, and sinterization processes that involved the handling of fine powder. Approximately 68% of the reported cases of manganism were exposed between 1 and 2 yr, although 6 cases were observed in men exposed between 1 and 3 mo. Based on his observations, Rodier (1955) hypothesized that workers with "less-than-healthy" lungs were most susceptible to Mn toxicity, but that high carbon monoxide levels experienced during mining activities might have also been involved in causing some of the neurological symptoms. Rodier (1955) concluded that medical screening of workers might prove useful, and recommended that exposures of workers to dusts be reduced.

Schuler et al. (1957) reported that 15/370 (4%) miners in a Chilean ore mine exhibited clinical neurotoxicity where exposure concentrations ranged from 0.5 to 46 mg Mn/m^3. The highest concentrations, as measured by an electrostatic precipitator, were observed in drillers working with pure, dry pyrolusite (MnO_2) ore. Psychomotor disturbances and neurological symptoms such as emotional instability, apathy, hallucinations, paresthesia, muscle weakness, and sleep disturbances were reported in the 15 miners; however, the exposure data were insufficient to estimate an internal dose of Mn for any of the miners. The authors reported that approximately one-third of the measured concentrations exceeded the MAC of 6 mg Mn/m^3 (of 39 measurements, 22 were below, 4 were in the range, and 13 were above the MAC). Abdel-Naby and Hassanein (1965) reported 45 cases of manganism in pyrolusite miners, 42 of whom were rock drillers. The duration of exposure to Mn ranged from 5 mo to 25 yr with a median of 9 yr. Although no exposure levels were reported, many of the cases of manganism were associated with dry-rock drillers, who were thought to have incurred significantly higher exposures during the dry-rock drilling period (1925–1952) than did the wet-rock drillers (1952–1963). Thirty-seven (82%) worked as dry-rock drillers, 5 (11%) worked as wet drillers, and 3 (7%) worked as porters loading broken pieces of Mn ore. None of the cases showed any improvement after removal from the mines, and neurological symptoms progressed even after cessation of exposure. Of interest in this study is that 15.5% of the cases were brothers or cousins; thus, the authors concluded that there might be a genetic component to manganism.

Chandra et al. (1974) studied 12 workers in a Mn mine in India and compared their symptoms to 20 healthy, unexposed control workers of approximately the same age. In the absence of any exposure information or concentration data, these investigators attempted to correlate symptoms of early Mn toxicity with serum and urine Mn concentrations. Mn concentrations in serum were found to be normal or only slightly elevated compared to controls, indicating that this measurement was of little value for detecting Mn toxicity. Serum calcium, on the other hand, was found to be statistically elevated; however, the mechanism and significance of this biochemical change, and the correlation to Mn toxicity, were not well understood. Even today, with the possible exception of a MRI for detecting Mn levels in the brain, there are no useful biological biomarkers for assessing past exposure to Mn or toxicity.

Despite the lack of understanding regarding the underlying cause, Cook et al. (1974) evaluated treatments for effectively reversing neurological symptoms in workers exposed to mean concentrations of 2.5 to 11 mg Mn/m^3. In their study of 6 affected workers at a Mn ore-crushing plant, Cook et al. (1974) administered edetic acid and L-dopa therapy and evaluated their efficacy for improving symptoms. Although edetic acid resulted in improvement of symptoms in 4 workers, and L-dopa therapy showed a possible response in 2 workers, the authors concluded that a clearly effective treatment for manganism was not identified or available.

Battery Workers Several studies of battery workers were conducted during this time period, but only one study identified in the literature evaluated both neurological effects and exposure levels. In their evaluation of dry-battery workers in Cairo, Egypt, Emara et al. (1971) performed a clinical examination and measured blood Mn concentrations of 36 workers employed at the facility between 1 and 16 yr. All workers exhibited symptoms such as headache, memory disturbances, sleep problems, mood disorders, impulsiveness or aggressiveness, and impotence or hypersexuality. Eight of the workers (22%) also indicated neuropsychiatric symptoms, and 6 of these workers were diagnosed with chronic Mn psychoses. Mean Mn concentrations (as MnO_2) ranged from 6.8 to 42.2 mg/m^3, which were higher than the TLV ceiling limit of 5 mg Mn/m^3. Blood Mn levels, though elevated (mean levels ranged from 0.02 to 2.3 μg/100 ml), were considered normal (normal ranges were not provided). The authors concluded, "The concentration of manganese dust in the air showed some association with the prevalence and rapidity of effect on workers according to their occupations. However, individual susceptibility was apparent."

Plant and Factory Workers Several studies of plant workers, particularly those working with alloys and other metals, were published during this time frame (Whitlock et al., 1966; Tanaka & Lieben, 1969; Smyth et al., 1973; Suzuki et al.1973a, 1973b; Saric et al., 1977). In Japan, 160 ferromanganese alloy workers exposed to <1 to 4.86 mg Mn/m^3 were evaluated for neurological symptoms (Suzuki et al.1973a). Subjective symptoms, such as fatigability, impotence, and decreased memory were observed in approximately 30% of the workers, and 24% of workers exhibited finger tremors. The symptoms were generally more frequent in those having the longest service period, or among workers in the electric furnace room. As a result of these findings, a follow-up study of 100 electric furnace workers was conducted (Suzuki et al., 1973b). The same subjective symptoms were observed in 40% of these furnace workers. Mn exposure levels were higher among these workers (3.2–8.6 mg Mn/m^3), but urinary and blood Mn concentrations, though above normal, were lower than the entire group of ferromanganese alloy workers. The authors noted that dust concentrations were higher in working-room air during tapping of Mn ore, where dust concentrations were reported to be $>10{,}000$ particles/cm^3.

As mentioned previously, two comprehensive studies were conducted during this time period that permit an evaluation of the association of Mn exposure with adverse neurological effects (Tanaka & Lieben, 1969; Smyth et al., 1973). Tanaka and Lieben (1969) evaluated workers from 75 plants who handled various materials, including steel castings, nonferrous metal castings, metal manufacturing, ceramics and brick facilities, manufacturing (including of dry-cell batteries), and Mn or ferromanganese ore processing. While historical Mn concentrations at these plants were estimated to be in excess of 100 mg Mn/m^3, measured mean concentrations ranged from 1 to 27 mg Mn/m^3. Clinical neurological exams were conducted for workers in 12/75 (16%) plants where concentrations were near or above 5 mg Mn/m^3 (the contemporaneous TLV), as well as some plants

where exposures were lower. The neurological screening examination included 33 symptoms and signs for detecting neurotoxicity or manganism, including muscle weakness or stiffness, fatigue, insomnia, sudden laughter or crying, stuttering, forgetfulness, gait disturbance, inability to walk backward, expressionless face, speech difficulties, hand tremor, and abnormal reflexes. Urine was also collected from some workers. Industries with excessive Mn exposure levels (i.e., above the TLV) included plants involved with steel castings (8.4% above TLV), metal manufacturing (9.1%), ceramics and brick plants (16.7%), and ore processing (100%). Of the 117 workers from plants with excessive exposure, 7 (6%) were found to display definite symptoms of neurotoxicity. Two of the workers with the highest exposures had been exposed in Mn ore-crushing mills, 1 from arc burning of an 11% Mn steel; 4 of the highest exposed men worked in a large steel plant that casted and crushed ferromanganese alloys. Neurological symptoms were found to improve in the steel worker after chelation therapy. In comparison, in workers exposed to <5 mg Mn/m^3, no apparent clinical symptoms of neurotoxicity were observed. With regard to biomarkers, the authors found some correlation between mean group urinary Mn levels and mean air concentrations; however, no association could be made between urinary concentrations and observed symptoms. The authors stated that this was likely due to the fact that urinary measurements reflected recent exposure, while clinical symptoms were more likely related to chronic exposures. The authors discussed how Mn exposure differed with various industries; for example, processing of Mn ore and ferromanganese alloy provided the main source of exposure to Mn during crushing, pulverizing, and bagging. The next highest exposure occurred in chemical manufacturing plants, such as for dry-cell batteries and gas masks, in which MnO_2 was the primary form of Mn. In the ceramic and brick industries, Mn compounds were added as coloring agents and exposure occurred intermittently at the time of dumping, weighing, and mixing the ingredients. Another source of Mn exposure in brick plants or stone crushing plants was welding and repair work on high Mn steel.

Smyth et al. (1973) conducted a reappraisal of the environment and health of 71 employees of a Pennsylvania ferromanganese processing and product facility. Interestingly, this facility was also included in the Tanaka and Lieben (1969) study. Workers primarily worked with or around a blast furnace into which molten ferromanganese alloys were poured, or in the crushing and screening process, which began in 1957. This study encompassed three phases of investigation, including the nature of exposure, epidemiology, and adverse health effects. In the first phase, Mn samples were collected on six different occasions between 1959 and 1964. Results indicated that Mn concentrations were in excess of the TLV much of the time, with short-term concentrations measured in the breathing zone of crushers and crushers' helpers ranging from 3.2 to 80 mg Mn/m^3 when ventilation was absent. Air concentrations of Mn (based on area samples) at the crusher discharge ranged from 405 to 1750 mg/m^3, while air concentrations at the screening station varied from 27 to 350 mg/m^3. In 1960, after the installation of a ventilation system, Mn dust concentrations at the crusher averaged 0.6 to 0.7 mg/m^3. As noted by the authors, the TWA concentrations would be significantly lower and likely below the TLV of 5 mg/m^3; however, short-term samples in the breathing zone of the crushers were markedly elevated, and sometimes higher than the proposed ceiling limit. In February 1966, based on results of the exposure measurements, the second phase of the study was implemented.

The second phase involved the evaluation of fume and dust exposures at 15 positions in the processing and production areas. None of the studied employees were stationed in the crusher area. Unlike earlier studies, Smyth et al. (1973) conducted detailed analyses on the composition of Mn fume and dust to allow for the evaluation of exposure. All of the fume was composed of Mn oxide, mainly as hausmannite (Mn_3O_4), and was less than 2 μm in size (i.e., respirable). Mn fume concentrations at the blast furnace cast house and pig-casting machine ranged from 3.02 to 206 mg/m^3, with TWAs ranging from 0.12 to 13.3 mg/m^3. The number of samples exceeding the STEL ranged from 0 to 93%. The dust was mainly composed of ferromanganese, with small amounts of manganosite (MnO), Mn_3O_4, and iron oxide (Fe_2O_3). Approximately 95% of the dust was <5 μm in size, and concentrations ranged from 0.18 to 61.5 mg/m^3, with TWAs ranging from 2.1 to 12.9 mg/m^3. The number of samples exceeding the STEL of 5 mg/m^3 ranged from 3 to 70%.

Because of the high exposure concentrations observed, Smyth et al. (1973) conducted a clinical phase wherein the health effects were evaluated in 71 workers. A neurologist examined all employees,

and blood and urine samples were obtained. Five cases (7%, 3 exposed to Mn fume and 2 to Mn dust) were observed with CNS impairment suggestive of manganism, such as masked face, loss of arm movements, tremors, and rigidity. All five were from the "exposed" group, and all but one occurred in areas with the highest Mn concentration. After 3 mo, symptoms improved in 2 of the cases, but the same degree of neurological deficit was seen in 3 cases with no improvement or deterioration. No significant differences were observed in blood Mn levels between the exposed and control groups; urine concentrations in the exposed group were threefold higher than in the unexposed group, but were not correlated to airborne Mn concentrations. The authors concluded, "Although parkinsonism[13] and manganism are indistinguishable, the detection of 5 cases among persons having occupational Mn exposure, and in an age group in which parkinsonism is not expected, justifies the presumption of a causal relationship [between Mn exposure and manganism in these workers]. The mobilization and excretion of large amounts of stored Mn after treatment with calcium EDTA supports this presumption."

Welding Studies A few studies of welders began to appear in the published literature during this period. Smith (1967) conducted a study of metal fume exposure during low-hydrogen electrode welding in various industrial settings classified as confined (<2000 ft^3), enclosed (>2000 ft^3), and open conditions (open air). The author noted that low hydrogen electrodes were often used for "difficult-to-weld" steels. Mn samples were collected in the welders' breathing zone with and without exhaust systems in place. Results indicated that 75% of samples taken in the confined spaces, 50% of enclosed samples, and 27% of open-air samples exceeded 10 mg Mn/m^3. For the confined and enclosed spaces, mean exposure concentrations were markedly reduced when exhaust systems were present. Health effects were not evaluated in this study.

Other studies describe Mn exposure concentrations potentially experienced by welders. For example, Tanaka and Lieben (1969) observed one case of "manganese poisoning" in a worker involved in the arc burning of Mn steel. They reported that most air samples collected during welding and burning operations were less than 5 mg/m^3 when the material being manipulated contained less than 1% Mn. In fact, all measurements over 5 mg/m^3 were associated with steel containing 10–15% Mn. Despite the discussion of welders in some reports, few studies were conducted to evaluate neurological effects in welders until the 1980s.

1980–Present: Shift in Focus to Welders

From the early 1980s to the present, there has been a shift in focus from assessing clinical effects in the "high Mn exposure" populations (miners, millers, and plant workers) to evaluating possible subclinical effects in the "low Mn exposure" occupations such as welding. It is important to note that, in general, these studies typically reported subclinical neurological effects in asymptomatic workers (Chandra et al., 1981; Kondakis et al., 1989; Wennberg et al., 1991; Hochberg et al., 1996; Sjögren et al., 1990, 1996; Luse et al., 2000; Sińczuk-Walczak et al., 2001). Several studies during the last two decades reported estimated thresholds for neurological effects in workers exposed to Mn (and often other compounds) in settings such as smelters, factories, dry alkaline battery manufacturing facilities, and ferromanganese alloy production plants (Roels et al., 1987a, 1992; Wang et al., 1989; Iregren, 1990; Hua & Huang, 1991; Chia et al., 1993a, 1993b; Kaji et al., 1993; Kim et al., 1994, 1999, Mergler et al., 1994; Lucchini et al., 1995, 1997; Huang et al., 1998; Gibbs et al., 1999). By the late 1980s and early 1990s, research efforts focused on refining exposure measurements and detecting early neurological and/or neurobehavioral effects in exposed workers. Mn levels were reported in studies of various workers conducted in the latter part of the

[13]"Parkinsonism" is a term that is used to describe a condition that causes any combination of the types of movement abnormalities seen in Parkinson's disease. The symptoms of parkinsonism include tremor, bradykinesia, rigidity, and postural instability or impaired postural reflexes. Idiopathic PD is the most common cause of parkinsonism and is thought to account for more than two thirds of the cases. Parkinsonism can result from many other disorders, such as hereditary diseases (e.g., Wilson's disease), multiple system atrophies (e.g., Shy–Drager syndrome), other degenerative diseases (e.g., Creutzfeldt–Jakob disease), other CNS disorders (e.g., tumor), infections (e.g., viral encephalitis), exposure to toxins (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], carbon monoxide), metabolic disturbances (e.g., hepatocerebral encephalopathy), and the use of medications (e.g., neuroleptics) (Stacy & Jankovic, 1992). Manganism is considered by some investigators to be a form of parkinsonism because the disorder involves abnormal motor movements.

20th century, where airborne Mn levels associated with an increased incidence of subclinical neurological symptoms such as alterations in reaction time, short-term memory, and eye–hand coordination ranged from 0.027 to 1 mg/m^3 (Roels et al., 1987a, 1992; Iregren, 1990; Wennberg et al., 1991; Chia et al., 1993a, 1993b; Mergler et al., 1994; Lucchini et al., 1995; Park et al., 2006).

Few studies tested subjects for subclinical symptoms at exposures below 0.2 mg Mn/m^3, and those studies that did typically reported no change in neurological effects. For example, Deschamps et al. (2001) did not detect increased adverse neurological effects in 138 enamel workers exposed to mean respirable levels of 0.057 mg Mn/m^3 for an average of 20 yr. In contrast, other studies indicated that exposure to total airborne dust concentrations below the contemporaneous ACGIH TLV of 5 mg/m^3 for less than 20 yr may still lead to subclinical signs of neurotoxicity (Roels et al., 1992). In this latter study, geometric mean concentrations of respirable and total dust were 0.2 mg/m^3 and 1 mg/m^3, respectively. Additionally, a recent study of welders reported subclinical neurobehavioral impairments associated with exposures below the TLV of 0.2 mg/m^3 (Park et al., 2006); however, clinical signs of Mn intoxication are seldom reported at exposure levels below 5 mg Mn/m^3 (Tanaka & Lieben, 1969; Saric et al., 1977; Chandra et al., 1981; Deschamps et al., 2001; ACGIH, 2001).

"High-Exposure" Studies Studies of miners in the 1950–1980 time period indicated that Mn exposures experienced by these workers, particularly dry-ore drillers and processors, exhibited Mn-induced symptoms (Rodier, 1955; Schuler et al., 1957; Abdel-Naby & Hassanein, 1965; Greenhouse, 1971; Chandra et al., 1974; Cook et al., 1974); however, in later years, fewer adverse neurological effects were reported in Mn miners, likely as a result of improved industrial hygiene activities to reduce Mn exposure levels. For example, Hochberg et al. (1996) evaluated 59 workers in a Chilean mine in a blinded control study to examine late-life motor deficits. Many of these workers were stated to have heavy dust exposure while working in the mines for 5 yr or longer, yet the exposed group displayed few neurological symptoms. Resting and action tremors were observed in the exposed group more frequently than in controls, and the authors concluded, "Chronic asymptomatic Mn exposure results in detectable late-life abnormalities of movement." A large cross-sectional study of 489 African mine workers concluded that miners exposed to MnO_2 at concentrations near the TLV were "unlikely to have a subclinical neurotoxicity problem" (Myers et al., 2003a); however, this largely null study did not focus on drillers or other mine workers intimately involved in processing Mn ore. Instead, the workers included not only underground miners and surface processors, but office workers, engineers, and related service workers. In their studies of Mn millers from 1981 to 1991, Chia et al. (1993a, 1993b) measured Mn levels in the air ranging from approximately 0.06–6 mg/m^3, with a mean concentration of 1.59 mg Mn/m^3. The Mn levels progressively declined during this time period. Neurobehavioral effects observed in workers included decreased motor speed, visual scanning, and visuomotor response and coordination. Although these were reported more frequently in exposed workers, they were also reported in nonexposed workers, and clinical examinations showed no remarkable difference between the exposed and nonexposed groups.

Battery workers continued to be of interest during this time period (Sumitra & Kongsombatsuk, 1990; Gennart et al., 1992; Roels et al., 1992, 1999; Bader et al., 1999; Hanley & Lenhart, 2000; Sińczuk-Walczak et al., 2001; Dietz et al., 2001). In Thailand, exposure concentrations measured using x-ray fluorescence in a dry-cell battery manufacturing facility ranged from 0.02 to 41.1 mg Mn/m^3 (Sumitra & Kongsombatsuk, 1990), whereas German investigators found concentrations of 0.001 to 0.79 mg Mn/m^3 in dust (Bader et al., 1999). In the latter study, MnO_2 constituted 3 to 46% of the respirable dust. In a battery plant in Belgium, a median of total Mn dust concentrations of 0.71 mg/m^3 was measured (Gennart et al., 1992). This study focuses only on reproductive effects, not on neurological effects, reporting no statistically significant decreases in fertility. In a U.S. study at an alkaline battery plant, investigators found total Mn concentrations in the personal breathing zone of workers ranging from 0.1 to 5.4 mg Mn/m^3, with 6 to 32% of the particulates being respirable. The use of respirators reduced 8-h TWA concentrations to less than 0.05 mg Mn/m^3 (Hanley & Lenhart, 2000). Although this study focuses primarily on respirator performance, the authors note that the investigation was conducted following a report of neurological effects and "manganism symptoms" in the battery workers. No further details on health effects were provided.

In Belgium, a prospective study reported increased neurobehavioral deficits in 92 workers in a dry alkaline battery manufacturing facility with concentrations of respirable Mn oxide of 0.021 to 1.317 mg/m^3, with a mean of 0.3 mg Mn/m^3 (Roels et al., 1992, 1999). Approximately 90% of workers were exposed to levels less than the TLV of 5 mg Mn/m^3. While exposed workers performed worse than controls on neurofunctional tests (e.g., eye–hand coordination, hand steadiness, and simple visual reaction time), these workers did not differ from controls on reported neuropsychological symptoms and performance on audioverbal short-term memory tests. Based on their results, Roels et al. (1992, 1999) concluded that exposure to total airborne dust below the contemporaneous TLV (5 mg/m^3) for less than 20 yr might still lead to subclinical signs of Mn intoxication. Similarly, based on their evaluation of 13 battery workers and 62 welders employed in the same shipyard, Sińczuk-Walczak et al. (2001) concluded, "Mn exposures within the <0.01–2.67 mg/m^3 range . . . induce[d] subclinical effects on the nervous system." Neurological symptoms in these workers included increased irritability, decreased memory, concentration difficulties, sleepiness, and limb paresthesia; however, there was no correlation between percentage of workers reporting adverse effects and airborne Mn levels, and the clinical data for individual groups of workers were not reported separately.

Finally, plant and factory workers in facilities with ferromanganese or silicomanganese alloys (Wang et al., 1989; Huang et al., 1989, 1993, 1998; Hua & Huang, 1991; Kim et al., 1994; 1999 Mergler et al., 1994; Lucchinni et al., 1995, 1999), refining (Kaji et al., 1993), and in smelters and foundries (Iregren, 1990; Wennberg et al., 1991; Myers et al., 2003b) continued to be of interest during the latter part of the 20th century. Many of these studies attempted to correlate biological markers, such as Mn blood and urine concentrations, to airborne concentrations of Mn in fume and dust, although few significant correlations were found. One of the larger studies indicated that early stages of clinical neurotoxicity, defined as observance of nonspecific effects (such as headache, insomnia, anorexia, apathy, and spasms) or psychological and psychomotor changes, could be detected in population studies if sensitive testing methods were employed (Mergler et al., 1994); however, despite observable patterns of response resulting from Mn toxicity, no dose-response relationships could be established among the 115 ferro- and silico-manganese alloy production workers studied in this investigation. Another large study on nervous system effects in 509 smelter workers concluded that their results demonstrated only weak and unconvincing evidence for a dose-response relationship (Myers et al., 2003b).

Lees-Haley et al. (2006) conducted a meta-analysis of 20 peer-reviewed published neuropsychological studies that evaluated the cognitive, psychological, motor, and sensory/perceptual effects of exposure to Mn in 1410 exposed participants and 1322 controls. These studies included Mn workers employed in a variety of industries, including Mn milling and mining, Mn ferroalloy plants, MnO_2 salt plants, and battery manufacturing. The authors focus on neuropsychological effects, because many studies of Mn-exposed workers were conducted to evaluate those endpoints in asymptomatic workers to develop early detection methods or measures of "subclinical" phenomena. Some investigators believe that neuropsychological tests are more sensitive than neurological tests, and that subtle deficits detected by neuropsychological testing are precursors of more serious, clinical neurological effects such as manganism (Iregren, 1994; Mergler et al., 1994); however, there is much debate in the scientific community about this. Dose-response relationships were evaluated for neuropsychological effects and several parameters, including (1) measures of Mn levels in air and dust, (2) reported years of exposure, (3) blood Mn levels, (4) urine Mn, and (5) hair Mn. A statistically significant weighted mean effect size of –0.17, suggestive of impairment, was calculated for neuropsychological symptoms and Mn exposure (defined as exposed to Mn at the time of the respective study). An effect this small is typically undetectable when evaluating workers on an individual basis. There were no significant associations between neuropsychological effects and (1) years of exposure, (2) levels of Mn in air, (3) Mn concentration in blood, or (4) Mn levels in urine. The authors concluded that occupational exposure to Mn at levels that typically occur in the milling and mining, ferroalloy, MnO_2 salt, and battery manufacturing industries probably may exert a small deleterious effect on cognitive and sensory motor performance, which may be detectable in population studies; however, it is generally too small to be detected in any one individual through current clinical assessment, and it is not clear that such an effect possesses any clinical significance.

A hospital-based case-control study in South Korea was conducted by Park et al. (2005) to evaluate the role of occupational exposure to Mn as a cause of PD and whether any associations exist between various occupations and PD. Three hundred sixty-seven PD patients and 309 controls were interviewed about occupational history, lifestyle, family history, and education level. The investigators reported that Mn exposure was not a risk factor for PD and that occupations with potential exposure to Mn, such as welders, smelter workers, welding rod manufacturers, Mn miners, workers in the iron and steel industries, and dry cell battery manufacturers showed consistently negative associations with PD after adjusting for the confounders such as age, gender, smoking, and education level.

Studies of Welders Numerous studies of welders began to appear after 1980 (Chandra et al., 1981; Anatovskaia, 1984; Yim et al., 1998; Järvisalo et al., 1992; Sjögren et al., 1990, 1996; Jin et al., 1999; Kim et al., 1998; Moon et al., 1999; Korczynski, 2000; Luse et al., 2000; Sińczuk-Walczak et al., 2001; Bowler et al., 2003, 2006a, 2007; Lees-Haley et al., 2004, 2006; Racette et al., 2005; Halatek et al., 2005; Park et al., 2006; Rohling and Demakis, 2007); however, during the last 100 yr, there have only been approximately fifteen case reports of clinical neurological symptoms in welders (Belniker, 1932, as cited in Fairhall & Neal, 1943; Whitlock et al., 1966; Tanaka & Lieben, 1969; Rasmussen & Jepsen, 1987; Wang et al., 1989; Nelson et al., 1993; Franek 1994; Barrington et al., 1998; Kim et al., 1998; Sato et al., 2000; DiScalzi et al., 2000; Ono et al., 2002; Sadek et al., 2003; Koller et al., 2004; Josephs et al., 2005). Most of these cases involved very high exposures over long periods of time, with little or no ventilation and/or personal protection (Table 3). Most of the studies conducted with welders have been designed to evaluate respiratory effects. Pulmonary effects including metal fume fever, bronchitis, lung function decrements, increased susceptibility to infection, and a possible increase in the incidence of lung cancer have all been reported in welders; however, much less information is available concerning the non-respiratory effects (e.g., neurological) of welding fume exposure (Antonini et al., 2006).

Cross-Sectional Welder Studies Most of the studies that have been conducted to date to evaluate neurological effects in welders have been cross-sectional in design. Cross-sectional studies are conducted to collect data on exposure and health endpoints at one particular point in time, to provide a snapshot of the variables of interest in the study (e.g., Mn exposure and neurotoxicity). These studies are descriptive and may provide information about an association between variables, but do not confirm the existence of a causal relationship. The cross-sectional studies that have evaluated neurological effects in welders, along with case reports of welders that have reported neurological effects, are shown in chronological order in Figure 4.

Chandra et al. (1981) conducted a survey of 60 welders and 20 unexposed control subjects from 3 facilities in India, to evaluate Mn exposure levels, self-reported physical complaints, and serum and urine Mn levels. Different welding conditions and activities occurred at each facility, and Mn levels ranged from 0.44 to 2.6 mg Mn/m^3. The authors concluded that Mn exposure produced neurotoxicity, based on (1) the reporting of more "nervous system" effects (brisk reflexes and tremors) in welders and (2) apparently higher urine Mn and serum calcium levels in the welders with positive neurological changes as compared to controls. The presence of neurological symptoms did not correlate with the duration of exposure to welding fume.

Anatovskaia (1984) surveyed the neurological status of 54 welders, 92 foundry workers, and 34 grinders with chronic bronchitis at an occupational health clinic in Russia (Antonini, 2003). Workers in all three groups reported a variety of subjective neurological symptoms such as dizziness, irritability, fatigue, weakness, numbness in the extremities, and memory loss. The author reported that the degree and frequency of the symptoms were associated with the severity of bronchitis; however, there was no information about types of exposures, exposure levels, duration of employment, or other potentially confounding variables. The fact that workers in all three groups reported symptoms indicates that the neurological effects were not necessarily due to welding.

A study by Sjögren et al. (1990) reported that welders exposed to Mn, lead, or aluminum reported more subjective neuropsychiatric symptoms on a questionnaire than welders apparently exposed only to chromium or nickel. The authors concluded that the neuropsychiatric symptoms were due to Mn, lead, or aluminum exposure in the welders, although exposure levels were not

TABLE 3. Case Reports of Welders with Neurological Effects

Reported Health Effects	MRI	Blood/Urine Mn	Work History	Mn Exposure	Reference
"Manganese poisoning"	None	None	Two German electro-welders	No exposure data provided Electrodes contained Mn	Belniker 1932 (as cited in Fairhall and Neal 1943)
"Apparent manganese poisoning" with progressive deterioration of motor activity, cerebration, and skilled coordination; progressive weakness; unsteadiness of gait; waxy facial expression; and weakness of facial musculature.	None	Urine Mn (spot sample, prior to treatment): 4.58 µg/l and 5.48 µg/l[a] Urine Mn (during treatment with Ca EDTA): up to 145 µg/l and ~1,000 µg/l	56-year old and 44-year old workers who cut and trimmed Mn steel castings in a small enclosure with an air-arc burner[a]	Air concentrations measured after workers removed from exposure: 0.1–4.7 mg/m^3 Steel castings contained Mn of unknown concentration	Whitlock et al. 1966[a]
"Parkinsonian symptoms"	None	None	Arc welder in a Pennsylvania steel plant	Welder worked on steel that contained 11% Mn Air concentrations during welding and burning operations were less than 5 mg/m^3 when the material worked on contained less than 1% manganese All measurements over 5 mg/m^3 were associated with steel containing 10 to 15% manganese	Tanaka and Lieben 1969
"Organic psychosyndrome accompanied by symptoms of parkinsonism"	None	None	Two manual metal arc welders in a boiler factory in Denmark with "poor" hygienic conditions, working for 17 and 31 years, respectively	Authors presumed that exposure to Mn exceeded 0.3 mg/m^3	Rasmussen and Jepsen 1987 (article in Danish with English abstract)
Parkinsonism	None	All but one worker showed "raised" blood Mn (> 20 µg/l)	Eight workers performing electrode fixation or welding during 1985	Workers exposed for 30 min/day, 7 days a week to "high" concentrations of Mn (>28.8 mg/m^3) during breakdown of ventilation system	Wang et al. 1989
Hemisensory deficit, weakness of the right arm and leg, hyper-reflexia of the lower extremities, severe headache, and irritability	MRI showed intense signals in basal ganglia and midbrain	Blood Mn: 0.018 µM (normal = 0.006–0.015 µM) Urine Mn (after EDTA treatment): 17 µg/day (normal: 0.3 µg/day)	44-year old arc welder Welded Mn steel alloy railroad track for 25 yrs, welding indoors without ventilation for 15 years	No exposure data Used welding rods of Mn-steel alloy and hot carbon cuttings of castings of a 20% Mn alloy; railroad tracks were 11–14% Mn	Nelson et al. 1993

(*Continued*)

TABLE 3. (*Continued*)

Reported Health Effects	MRI	Blood/Urine Mn	Work History	Mn Exposure	Reference
"Classic signs and symptoms of long-term Mn exposure" in one of two welders (no other details provided)	None	Serum Mn was "elevated": 11.3 μg/L[b]	Case 1: Welded fabricated steel beams indoors for construction of steel building; beams were 0.05–2% Mn (no symptoms) Case 2: Railroad track welder who used rods containing 2–25% Mn to weld tracks	Mn fume samples obtained "during workshift" for 2 welders (no other details): 0.32 and 0.73 mg/m^3 Mn fume, respectively Mn fume sample when welding a railroad frog for 12 and 15 min: 4 and 7.2 mg/m^3 Mn fume	Franek 1994
Manganese encephalopathy with dementia affecting memory and executive function, postural instability, intention tremor, sensory deficits (Case 1) Irritability, headache, dizziness, decreased memory, schizoid traits (Cases 2, 3, 4, and 5)	"Typically" transient findings of increased signal in basal ganglia; hyper-intense signal in globus pallidus	Range of blood Mn for welders: 0.9–2.0 ng/ml (laboratory reference range: 0.4–0.85 ng/ml) Range of urine Mn for welders (post-EDTA treatment): 17–37 μg/day (laboratory reference: <0.3 μg/day)	Study of workers in a railroad "frog" shop, including 5 welders. Cases 1, 2, and 3: Welder of railway track frogs and connectors Case 4: Performed outdoor, onsite welding and repair with Mn alloy track Case 5: Welder working on variable tasks with mild steel	Case 1, 2, 3, and 4: Railroad track frogs and connectors made of 11–15% Mn; welding rods made of 11–25% Mn alloy Case 5: Mild steel contained 1–2% Mn Airborne Mn measured in breathing zone 10 years prior to diagnosis ranged from 0.0035–1.4 mg/m^3 (79–219 min)	Barrington et al. 1998
Neurological symptoms including masked face, right side resting tremor, bradykinesia; diagnosed with idiopathic parkinsonism	MRI showed symmetrical high signal intensities in globus pallidus and midbrain	Blood and urine Mn measured two months after cessation of exposure Blood Mn: 3.26 μg/dl (normal <2 μg/dl) Urine Mn: 3.57 μg/l (normal = 2 μg/l)	48-year old welder who welded 2 hr/day for 10 years in several workplaces and 10 hr/day for two years	Personal exposure levels to Mn fume (personal exposures measured outside welding shield) in 5 other welders were: Mean: 0.63 mg/m^3 Range: 0.34–0.86 mg/m^3 Mn fume (personal exposures measured inside welding shield) in two of the welders were 51.2% and 70.6% of the levels measured outside the shield.	Kim et al. 1998
Neurologic findings included dystonia, masked face, bradykinesia, rigidity, and retropulsion	MRI showed hyperintensity lesions in the bilateral globus pallidus, midbrain, dentate nucleus, and cerebral white matter; reduced in size and density after 10 mos	Not reported in abstract	56-year old welder who worked for 30 yrs	No information	Sato et al. 2000 (abstract; article in Japanese)
Postural tremor, muscular hypertonia, and bradykinesia; diagnosed with idiopathic parkinsonism	MRI showed symmetric paramagnetic deposits in the basal ganglia and midbrain; symmetric abnormal	Blood Mn: 14.4 μg/L (before treatment) and 8.2 μg/L (after treatment)[a] Urinary Mn: 1.71 μg/day (before treatment), up to	53-year old welder who welded for approximately 30 years; worked in "electrode fixation"	No exposure data Had worked in "electrode fixation," a task potentially associated with higher exposure to welding fumes	DiScalzi et al. 2000

	signal hyperintensity in substantia nigra and globi pallidi	27.8 µg/day (during treatment) and 0.1 µg/day (after treatment)[b]		Mn concentration in iron alloys and welding rods routinely used in welder's job contained 0.54% and 1.39% Mn, respectively	
Myoclonic involuntary movement in the right upper and lower extremities without parkinsonism	MRI revealed symmetrical high-intensity signals in the globus pallidus to the cerebral peduncle	Blood Mn was "elevated": 4.3 µg/dl (normal = 0.8–2.5 µg/dl) Urinary Mn: <1 µg/dl	17-year old electric arc welder who welded for 2 yrs	No exposure data	Ono et al. 2002
Cognitive slowing, rigidity, tremors, slowing of movements, gait instability leading to falls, saccadic eye pursuit, hypomimia, cogwheel rigidity, and cock-walk gait. Diagnosed with "parkinsonism due to manganism"	MRI showed increased signal intensity in basal ganglia and globus pallidus bilaterally	Serum Mn "elevated": 22.9 (normal = 8.0–18.7) Urine Mn "elevated": 3.1 (normal = 0–2.9) (no units provided, presumed to be µg/l)	33-year old welder; worked in shipbuilding industry for three years working in "confined ship's hold" doing steel alloy welding	No exposure data Used steel-Mn alloy and frequently welded in closed compartments in ship hulls	Sadek et al. 2003
All 13 welders were diagnosed with "Manganese-induced parkinsonism" Tremor (resting, postural, or kinetic), bradykinesia, rigidity, postural instability, and gait abnormality. No response to L-dopa therapy.	None	None	13 career welders (average length as welder = 25.2 yrs)	No exposure data Welders indicated history of working in confined spaces without adequate ventilation	Koller et al. 2004
Headaches, mood changes, transient double vision, memory loss, imbalance, tremor of head and hands, vertigo, slurred speech, myoclonic jerks, and reduced arm swing. Three of the cases were diagnosed with parkinsonism, although 2/3 cases had asymmetric reduced arm swing, which is more characteristic of idiopathic PD.	All 8 welders had bilateral hyperintense signals on T1-weighted MRI sequences in the globus pallidus in their initial MRI scan	Serum Mn levels were elevated in 7/8 welders - ranged from 0.8-1.3 ng/mL; (normal = 0.4-0.85 ng/mL).	8 welders referred to the Mayo Clinic with a variety of neurological complaints	No exposure data All of the welders performed MIG or TIG welding of stainless steel or galvanized steel. Authors reported, "chronic and intense exposure to ambient welding fumes and inadequate ventilation or other safety measures."	Josephs et al. 2005
Postural instability, Parkinsonism, dystonia, pyramidal signs	T1 sequences showed pallidal hyperintensity symmetrically at 4 and 17 months after onset of symptoms	None	32-year old welder with a 10-year history of welding in a shipyard	No exposure data	Kenangil et al. 2006

[a]Although these two cases were steel workers, rather than welders, this study is included in the table due to their work with arc welding and carbon electrodes for trimming manganese.

[b]Normal values not reported.

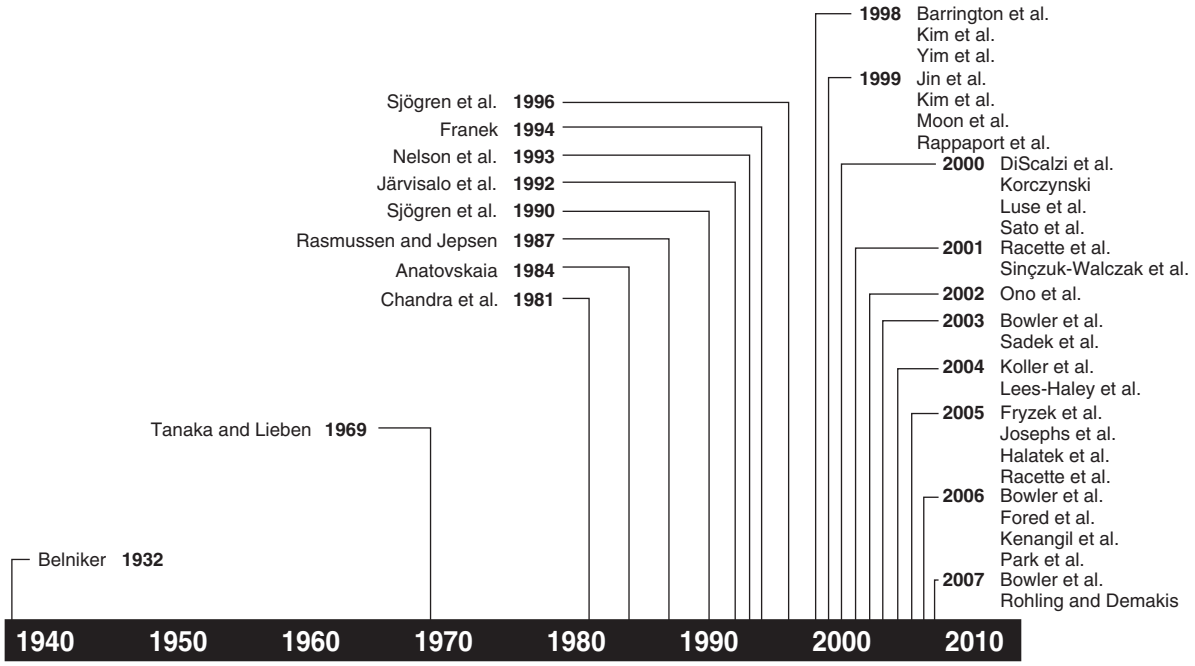

FIGURE 4. Timeline of studies and case reports evaluating neurological endpoints in welders.

provided. The questionnaire did not contain questions about family history or other potential exposures such as solvents or alcohol. Based on results from a battery of neuropsychological and neurophysiological tests, the same investigators reported that 12 welders with self-reported exposures to Mn showed more peripheral nervous system symptoms and sleep disturbances than unexposed control subjects (Sjögren et al., 1996). The welders did not have elevated blood or urine Mn levels, and no exposure data were provided, making it difficult to conclude anything about the reported neurological effects.

Three studies with welders were conducted in Korea to evaluate the MRI and neurological findings in welders (Yim et al., 1998) and the effect of duration of welding and neurobehavioral effects (Jin et al., 1999), and to determine whether airborne Mn levels correlated with Mn blood/urine levels and clinical signs of neurotoxicity (Moon et al., 1999). Yim et al. (1998) evaluated 35 welders from a bus-manufacturing facility by conducting brain MRIs and neurological examinations and obtaining blood and urine Mn levels. The mean duration of welding was 21 ± 5.7 yr. Twenty-seven (77%) of the workers had high signal intensities in the globus pallidus, and 11 workers (31%) showed subtle subclinical neurological abnormalities such as gait without associated arm movement, postural instability, and intentional tremor. The mean blood and urine Mn levels in the welders (2 and 2.5 μg/L, respectively) were below the nonexposed reference values in Korea (10 and 10 μg/L, respectively) (Yim et al., 1998). Welding fume and Mn levels were measured at 12 locations in 3 departments. The Mn levels ranged from 0.03 to 1.15 mg/m^3, which was reportedly above the permissible exposure limit of 1 mg/m^3. No other details were provided regarding the Mn sampling methods.

A neurobehavioral test battery and finger tapping were evaluated in 98 welders and 29 nonwelders from several factories (automobile manufacturing, automobile trailer manufacturing, steel frame manufacturing, or shipbuilding) (Jin et al., 1999). The welders were subdivided into three groups based on length of employment (1–10 yr, 11–20 yr, >21 yr). Mean Mn fume was reported to be 0.14 mg Mn/m^3 (ranged from 0.005 to 1.7 mg Mn/m^3) in shielded metal arc welding and was 2.1 mg Mn/m^3 (range 0.005–9.27 mg Mn/m^3) in CO_2 arc welding; however, cumulative Mn concentrations could not be estimated for the welders because of the lack of past ambient monitoring and the various types of welding performed by the workers. All categories of subjective neurological

symptoms and musculoskeletal symptoms increased with welding duration. Analysis of the correlation between subjective symptoms and neurobehavioral tests found simple reaction time, Santa Ana dexterity test with preferred hand and with nonpreferred hand, correct-dot and total pursuit aiming, and finger tapping with preferred hand and nonpreferred hand to be significantly correlated with muscle symptoms. Neurobehavioral tests such as finger tapping, digit symbol, and correct dot showed decreasing performance with increasing work duration, leading the authors to conclude that Mn exposure from welding is associated with "psycho-kinetic function decline." The report stated that neurobehavioral tests are appropriate tools for detecting early neurobehavioral abnormalities related to Mn exposure and that additional studies are necessary to confirm any correlations between Mn exposure and neurological effects.

Moon et al. (1999) conducted a study in which they (1) measured airborne, blood, and urine concentrations of Mn; (2) analyzed blood chemistry; and (3) observed clinical symptoms and signs for 60 welders and 60 age-matched controls in the same manufacturing industry (no details provided on specific industry type). A questionnaire and physical exam were used to evaluate neurological symptoms. Personal samplers were used to determine Mn levels over a 1-d period; the arithmetic and geometric means were 0.17 and 0.15 mg Mn/m^3, respectively. The blood Mn levels were not significantly different, while urine levels were significantly different between the two groups (2.52 vs. 1.89 μg/L); however, there were statistically significant correlations reported between Mn concentrations in blood and urine, airborne Mn and urine, and airborne Mn and blood. Subclinical effects such as headache, fatigue, general weakness, amnesia, excitation, speech disturbance, and nervousness were reported to be significantly higher in welders than in nonwelders (mean number of complaints 9.72 vs. 5.15).

Korczynski (2000) evaluated 128 welders by administering a questionnaire on respiratory effects and other miscellaneous health complaints. Eight different welding companies employed the welders, and Mn levels in fume at these locations ranged from 0.01 to 4.93 mg/m^3. Pain and fatigue were reported due to cramped and awkward conditions; no other apparent neurological effects were observed or reported in the welders. It is important to note that subjective symptoms such as pain and fatigue, which have multiple etiologies, have been interpreted as neurological effects associated with Mn exposure in some studies (Luse et al., 2000; Racette et al., 2005; Lees-Haley et al., 2004, 2006).

Sińczuk-Walczak et al. (2001) evaluated 13 battery workers and 62 welders and fitters employed in shipyard and electrical industries and concluded, "Mn exposures within the <0.01–2.67 mg/m^3 … induce[d] subclinical effects on the nervous system." The air samples were obtained in the breathing zone of subjects "during the effective working time (6–7 hr)," although details about the frequency of sample collection and number of samples were not provided. Neurological symptoms in these workers included increased irritability, decreased memory, concentration difficulties, sleepiness, and limb paresthesia; however, there was no correlation between percentage of workers reporting these subjective subclinical effects and airborne Mn levels, and the clinical data for individual groups of workers were not reported separately. Thus, it is not possible to make any conclusions specific to the welders regarding Mn exposure levels and the reported subclinical effects. In a subsequent publication, Halatek et al. (2005) reported the results of additional analyses of the same cohort of welders evaluated by Sińczuk-Walczak et al. (2001). The investigators evaluated neurological effects in 59 welders, matched for age and smoking habits with a control group of 23 mechanics and electricians not exposed to welding fumes. Subjective neurological symptoms, visual evoked potentials (VEP), and electroencephalography (EEG) were examined in welders, and the correlations between Mn concentrations in the air, blood, and urine as well as between cumulative exposure indexes (CEI) (Mn mg/m^3/yr of exposure) were investigated. The reported Mn ambient air concentrations ranged from 0.003 to 3.37 mg/m^3 in the welders and from 0.001 to 0.17 mg/m^3 in the control group. The mean blood Mn concentration was 11.4 μg/dl in the welders and 6.1 μg/dl in the control subjects. Abnormal VEP and EEG tests were reported in the youngest welders exposed to welding fumes and the changes were related to the highest Mn airborne levels (mean >0.3 mg/m^3) and high blood Mn concentrations. The investigators concluded that VEP and EEG tests may be used for the detection of early effects of exposure to low Mn levels.

Bowler et al. (2003) evaluated neuropsychological parameters in a group of 76 former and current chemical-industry welders involved in civil and workers' compensation litigation related to their impairments allegedly caused by welding. The authors reported that welders displayed more psychiatric symptoms and poorer scores compared to controls on tests of motor function, verbal fluency, cognitive flexibility, and visuospatial/visuoperceptual speed than 42 control subjects who were obtained from a telephone directory or were friends/neighbors of the welders. The authors acknowledged that welders were likely exposed to a variety of organic solvents, yet they concluded that the reported neuropsychological effects were due solely to Mn in welding fume. Most of the adverse health effects were based on subjective neuropsychological tests, and welding fume or Mn exposure levels were not reported. Clearly, there are concerns with the selection of subjects for this study, because it is recognized that personal injury claimants report experiencing significantly more neuropsychological symptoms than control groups (Dunn et al., 1995). The selection of controls from a local telephone directory or neighbors and friends of the welders also introduces significant concerns about the potential for bias. In addition, no attempt was made to correlate the abnormal neuropsychological findings with dose or duration or exposure (Jankovic, 2005). Lees-Haley et al. (2004) addressed many of the methodological problems associated with the Bowler et al. (2003) study, such as subject selection bias, response bias, and effects of litigation on symptom reporting and neuropsychological test performance. Their analysis of the Bowler et al. (2003) study in the context of whether the reported findings fulfilled any of the Hill (1965) criteria for evaluating causal associations concluded that, of the nine factors, only temporality was "weakly met" based on self-reported information (Lees-Haley et al., 2004).

A somewhat simplified version of the Bowler et al. (2003) study was conducted on another set of 47 San Francisco Bay Bridge welders who were referred to the investigator for neuropsychological and neurobehavioral examination (Bowler et al., 2006a). These welders were also involved in litigation regarding exposure to Mn. The results of the examinations on the welders were compared to the results from 46 controls from a previous study (Bowler et al., 2001) that had been chosen at random from a telephone directory "in one of the Southern states where many of the welders resided." The authors concluded that the welders performed poorly on tests measuring verbal and visuomotor speed of information processing, sustained concentration, and motor skills, resulting in a "higher prevalence of neuropsychological dysfunction in welders than in unexposed controls." However, comparing the results of the welders to data collected on control subjects that were not matched to the welders (e.g., age, socioeconomic status) from a different study conducted several years earlier is highly problematic and can introduce a significant source of bias into the results.

Park et al. (2006) conducted a study of 48 welders who were employed in the construction of a bridge in San Francisco. This is the same cohort of welders reported in the Bowler et al. (2003) study. Cumulative Mn exposures were estimated using results from 126 air samples (area and personal), and an exposure-response relationship was derived for 4 neurobehavioral tests. Using these results in a benchmark dose model, the study concluded that welders exposed at the current California standard of 0.2 mg/m^3 would experience an excess prevalence of neurological impairment. The authors concluded that the prevalence of attributable neurological impairment after the equivalent of 2 yr of exposure to 0.2 mg/m^3 is 15–32% and predicted 2–5% excess impairment after 2 yr exposure to 0.02–0.05 mg/m^3 Mn. Although the linear regression that the authors derived for the exposure-response relationships was statistically significant for some of the outcomes, the models explain only 8–21% of the overall variability, which is generally considered too low to be useful for predictions. This study evolved out of workers' compensation evaluations that were originally stimulated by public health reports of Mn health effects and litigation. The study did not have a matched control group, and instead compared results to "normal populations," and exposure measurements were not specific for individual welders. Park et al. (2006) conducted a battery of tests that took a full day to administer, but only presented results from four tests described as "a subset of 4 illustrative neurobehavioral tests were analyzed for risk assessment purposes." In addition, some important details are missing in this study, such as the workers' exposure conditions (time spent in chamber vs. pile), which could introduce bias, as the chamber Mn concentrations

were reported to be twice as high as the pile Mn concentrations. Other potentially confounding variables such as previous work history were not evaluated in this study.

Due primarily to a publication by Racette et al. (2001), the issue of welding as a possible risk factor for PD received increased attention in the press and scientific literature. Racette et al. (2001) conducted a cross-sectional study in which 15 male welders with parkinsonism who attended a movement disorders center were compared to two control groups of patients diagnosed with idiopathic PD. One control group was ascertained sequentially, and the other was gender- and age-matched to compare the frequency of clinical features and motor fluctuations. There were no clinical differences between the welders and the two control groups; however, welders had an earlier age of onset of parkinsonism than did the sequential control group, which consisted of 52 men and 48 women. The data led the authors to suggest that welding might be a possible risk factor for the development of early-onset PD. Racette et al. (2001) concluded that "a detailed clinical evaluation of career welders compared with age-matched controls in a proper epidemiologic study will be essential to prove the relationship between welding and parkinsonism." It is important to note that the majority (53%; 8/15) of the welders in the study had a family history of PD, a rate much higher than the 15% reported in unselected PD patients (Jankovic, 2005). The high frequency of family history is similar to young-onset PD cases, many of whom have a *Parkin* mutation, so it is likely that genetic factors, rather than welding, were the major risk factor in these relatively young patients with PD who happened to be welders (Jankovic, 2005). In addition, other epidemiological studies that have investigated occupation and/or Mn as a cause of PD have not established an association (Seidler et al., 1996; Tsui et al., 1999; Tanner, 2003; Gorell et al., 2004; Park et al., 2005).

Racette et al. (2005) conducted a study to estimate the prevalence of "parkinsonism" in welders in Alabama. They screened 1423 welders from Alabama who were referred for medical/legal evaluation for PD using videotaped assessments. The subjects provided information regarding exposure to welding fume and job titles. Using the number of active welders in this screening with parkinsonism as the numerator and the age-adjusted number of welders in each Department of Labor Standard Occupational Codes as the denominator, the prevalence of parkinsonism in Alabama welders was estimated and compared with general population data from a 1985 epidemiological study of Copiah County, Mississippi. No further details were provided about this study or the methods used to evaluate the Copiah County study subjects for neurological effects. The estimated prevalence of parkinsonism among active male welders statewide was reported to be 977 to 1336 cases per 100,000 population, depending on whether "conservative" or "liberal" definitions of parkinsonism were used in the Racette et al. (2005) study. The prevalence of parkinsonism was reported to be higher among welders in Alabama than age-standardized data for the general population of male residents of Copiah County from 1985. It is not possible to verify this conclusion, as the prevalence rate for the reference population was not provided. It is important to note that this study consisted of subjects that were referred to this clinic by attorneys involved in welding litigation, and the study was funded by the "Welder Health Fund," which was created by Gulf States Trial Attorneys to support medical/legal screening of welders.

There are many problems with the design of the study by Racette et al. (2005), including but not limited to: (1) a clear selection bias, because the welders were screened and referred to the study by plaintiff lawyers; (2) no proper control group (controls were from a 1985 survey of the entire population of Copiah County, Mississippi, conducted almost 25 yr ago, in a different geographic region with different demographics, using diagnostic techniques and methods different from those employed in this study); (3) extrapolation of the prevalence of PD from a single Mississippi county to the prevalence of parkinsonism statewide in Alabama; (4) use of an unvalidated video screening method that is not an accepted method in the medical community for diagnosing conditions such as PD, manganism, or parkinsonism; and (5) the absence of blindness of the examiners. In addition, the authors claimed that part III (motor examination) of the Unified PD Rating Scale was used even though this would require actual physical examination, which was performed in less than 7.9% of a "pseudorandom group" of subjects (Jankovic, 2005). Thus, this study cannot be relied upon to make conclusions regarding Mn exposure and development of manganism, PD, or parkinsonism.

Fryzek et al. (2005) conducted a retrospective cohort study of 27,839 male Danish metal-manufacturing employees from 1977 to 2001 to evaluate the risk of neurological disease among metal welders. The study, which was funded by current and former manufacturers of welding consumables, included workers who had been employed for a minimum of 1 yr during 1964–1984 in 1 of 79 selected iron and metal goods manufacturing companies with various types of metal-welding activities in Denmark. Of these, 9817 of the 27,839 workers had worked in welding departments and had potentially been exposed to welding fumes. Within this group, detailed information on occupational histories and tobacco smoking habits was obtained in 1986 by use of a self-administered questionnaire mailed to living workers or by interviews with next of kin or long-term colleagues of deceased workers. Using this information, those working specifically as welders were identified. The detailed information collected included first date ever employed in welding, type of welding (mild steel vs. stainless steel), use of ventilation, frequency of welding in small rooms, and smoking habits. The neurological disease experience of the cohort was identified by linkage with the Danish National Register of Patients, which maintained a computerized listing of all hospital admissions since 1977. The rates of PD and several neurological conditions, including secondary parkinsonism, degenerative diseases of basal ganglia, dystonia, or other extrapyramidal and movement disorders, were compared with those of the general population of Denmark. This study had a well-defined population with long-term follow-up, and the population and hospital registries cover the entire population of Denmark with a systematic ascertainment of PD and other neurological disorders (Fryzek et al., 2005). However, the authors state that their cohort did not include welders who may have had the highest exposure levels to welding fumes (e.g., welders in shipyards). The standardized hospitalization ratios for PD were 0.9 (95% confidence interval [CI] = 0.7–1.2) for men in steel-manufacturing companies, 1.0 (95% CI = 0.7–1.5) for men in welding departments, and 0.9 (95% CI = 0.4–1.5) for welders. The average age of first hospitalization for PD was not different among welders, and the observed numbers for other neurological conditions were small and not above expected values. Analyses for time period worked, age, and duration of welding were not significant. The results from this relatively large cohort study with long-term follow-up do not support the hypothesis that rates of hospitalization for PD or other neurological conditions are elevated in welders.

Fored et al. (2006) conducted a retrospective cohort study of 49,488 welders or flame cutters identified in the 1960 or 1970 Swedish National Census to compare the rate of basal ganglia and movement disorders in the welders to the rate in 489,572 age-matched and geographically matched employed men from the general population. A small subcohort of shipyard welders with potentially higher exposure levels for welding fumes was also identified and compared to the general population rates. A large survey to evaluate Mn exposure during welding (breathing zone and work site levels) at 70 different industrial sites and 21 railway track sections was conducted in Sweden during 1974–1975. The geometric means ranged from 0.13 to 0.3 mg/m^3 Mn and the highest detected levels ranged from 0.77 to 1.8 mg/m^3 Mn. However, information on the duration of employment was not available. Data on the cohorts were obtained from the Hospital Discharge Register, the Death Register, and to the Register of Population and Population changes. The cohorts were followed from January 1964 or January 1970 until the first hospitalization for a basal ganglia or movement disorder, date of emigration, date of death, or December 2003, whichever occurred first. The incidence rates of basal ganglia and movement disorders was 28 per 100,000 person-yr among the welders compared to 31 per 100,000 person-yr in the general population. The adjusted rate ratio was 0.91 (95% CI = 0.81–1.01) and was 0.89 (95% CI = 0.79–0.99) for PD in the welders and general population, respectively. There were no statistically significant increased or decreased adjusted rate ratios for any of the neurological disorders that were evaluated. Analyses by time period, geographical area of residency, welding in shipyards, and education yielded rate ratios close to 1.0. In addition, the mean age at first occurrence for PD was not different between the welder and flame cutter cohort (mean age 71.9 yr) and the comparison population (mean age 72 yr). This results from this study do not support a relationship between welding and PD or any other specific basal ganglia and movement disorders.

Case Reports of Welders Rasmussen and Jepsen (1987) reported that 2 Danish welders who had worked in "poor" hygienic conditions in a boiler factory for 17 and 31 yr, respectively, displayed

advanced stages of Mn toxicity, with symptoms of parkinsonism. No other exposure or clinical information was provided, making it difficult to draw any conclusions from this case report. Nelson et al. (1993) reported encephalopathy in a 44-year-old arc welder who had worked on Mn steel alloy railroad tracks (11%–14% Mn) for a total of 25 yr, 15 of which he worked indoors without any ventilation. Mn exposure levels were not reported. A diagnosis of Mn toxicity was made based on a blood Mn level of 0.018 μmol/kg (normal range 0.006–0.015 μmol/kg) and a urine Mn level of 17 μg/d (normal = 0.3 μg/d) 10 mo after employment ended, bringing into question whether there were other sources of Mn exposure or if he suffered from liver disease, which could compromise the clearance of Mn. An individual with liver disease may also exhibit neurological symptoms because of that person's inability to excrete Mn, resulting in an accumulation of excess levels of Mn (Ostiguy et al., 2005). Results from MRI showed intense signals in the basal ganglia, indicative of metal deposits, at termination of employment, which resolved within 6 mo, leading the authors to conclude Mn encephalopathy. A number of factors may induce encephalopathy, including solvent exposure or liver disease, both of which were not investigated thoroughly in this subject. Further, the signal observed in the MRI was not definitively identified as Mn.

A case report of an arc welder who had used welding rods containing 2–25% Mn while welding railroad tracks in a shop without respiratory protection indicated that he showed "classic signs and symptoms of long-term Mn exposure" (Franek, 1994). Very few details about his symptoms or diagnosis were provided, and he reportedly had an elevated serum Mn level of 11.3 μg/L. Normal ranges were not provided in this case report; however, normal Mn serum levels range from 0.15–4.3 μg/L (Saric, 1986; ATSDR, 2000). Two Mn fume samples were obtained "during workshift" and were reported to contain 0.32 and 0.73 mg Mn/m^3, but no information was provided about the locations of these samples. In addition, two Mn samples were obtained while the employee welded a railroad "frog," which is special track section where intersecting railroad tracks cross through each other and contains a high concentration of Mn. Levels of 4 and 7.2 mg Mn/m^3 for 12 and 15 min were measured, respectively. It is difficult to draw any conclusions from this case report, however, given the lack of detailed information about the worker's purported symptoms and historical exposure data.

Barrington et al. (1998) reported on a case series of workers in a railroad "frog" shop, including five welders and three machinists. This study arose due to the finding of Mn encephalopathy with dementia, postural instability, intention tremor, and sensory deficits in one welder ("index case"), leading to a more detailed investigation of other co-workers in the shop. The index case was discussed in detail by Nelson et al. (1993). Of the 5 welders evaluated, 3 of them worked with railway track frogs and connectors made of 11–15% Mn; 1 performed outdoor, onsite welding and repair with Mn alloy track; and the last welder worked on various tasks involving mild steel containing 1–2% Mn. In general, the welding rods used were made of 11–25% Mn alloy. The welders complained of irritability, headache, dizziness, and decreased memory, and exhibited schizoid traits. Airborne Mn measured in the breathing zone 10 yr prior to diagnosis for the index case ranged from 0.0035 to 1.4 mg/m^3 (sampling duration was 79–219 min). After the diagnosis of the index case, exposure levels were also measured, and calculated TWAs ranged from 0.08 to 0.44 mg/m^3 for welders, and 0.2 to 1.4 mg/m^3 for welders involved in outdoor grinding of metal. The range of blood Mn for welders was 0.9–2 ng/mL, but no correlations between Mn exposure and blood or urine Mn were found.

Kim et al. (1998) reported on a 48-yr-old welder who had welded 2 h/d for 10 yr in several workplaces, and spent 10 h/d welding at his last occupation for a period of 2 yr. The welder complained of neurological symptoms, which the authors diagnosed as idiopathic parkinsonism. Personal exposure levels to Mn fume for the welder were reported to be 0.63 mg Mn/m^3 (mean) and 0.34–0.8 mg Mn/m^3 (range). Reported blood and urine levels 2 mo after cessation of work were twice those of normal values.

Sato et al. (2000) reported that a 56-yr-old man developed postural instability and writing clumsiness after 30 yr of working as a welder. Neurologic findings included dystonia, masked face, bradykinesia, rigidity, and difficulty in retropulsion (walking backward). Brain MRI showed hyperintense lesions in the bilateral globus pallidus and other regions of the brain, which reduced in size and density after 10 mo. The diagnosis of Mn poisoning was attributed to the high Mn levels in both

serum and urine, and marked elevated urinary Mn level after administration of a chelating agent. No information about working conditions or exposure levels was provided in the abstract of this Japanese case report.

DiScalzi et al. (2000) reported that a 53-yr-old welder developed clinical signs of neurotoxicity such as postural tremor, muscular hypertonia, and bradykinesia. His occupational history included welding for approximately 30 yr. Exposure levels were not provided; however, the authors noted that he had worked for 26 yr in electrode fixation, a task potentially associated with a heavier risk of exposure to welding fumes. His Mn blood level was elevated (14 μg/L—normal range not reported), and the T1-weighted brain MRI showed signal hyperintensities that might be associated with the deposition of a paramagnetic metal in the basal ganglia and midbrain. He was removed from further occupational exposure and was provided chelating therapy, and approximately 6 mo later, the clinical pattern was greatly improved: His tremor had almost disappeared and his gait appeared normal.

Ono et al. (2002) reported that a 17-yr-old electric arc welder who had worked for 2 yr began to experience involuntary movement in the right upper and lower extremities. An MRI revealed symmetrical high-intensity signals in the globus pallidus, and his blood Mn level was elevated at 4.3 μg/dl (normal: 0.8–2.5 μg/dl); however, there was little detail about his work environment, and no exposure data were reported. Chelation therapy for 3 mo resulted in excretion of Mn in the urine, normalization of the Mn levels in the blood, and remarkable improvement of the myoclonic symptoms and MRI abnormalities.

Sadek et al. (2003) presented a case report of a 33-yr-old shipyard welder who frequently welded in closed compartments in ship hulls and was diagnosed with "parkinsonism due to manganism." He had welded for 3 yr, and the onset of symptoms occurred after only 1 yr, leading the authors to conclude that there was either an overwhelming exposure to Mn or other neurotoxic substances far in excess of established limits, idiopathic PD, or exposure to other neurotoxic substances outside of the workplace. Further, there was a reported history of PD in his maternal great aunt. A follow-up of this case reported that 3 trials of L-dopa were unsuccessful at sustainably reducing symptoms, and the former welder was displaying symptoms 2 yr after his initial diagnosis (Bowler et al., 2006b).

Koller et al. (2004) described a group of career welders (average of 25 yr) as having "manganese-induced parkinsonism," based on a reported lack of response to L-dopa and reported histories of working in confined spaces without adequate ventilation. The subjects were apparently "randomly selected from a cohort of patients examined for possible neurotoxicity from September 2001 to March 2002." Although they were not responsive to L-dopa, the subjects displayed atypical features for manganese-induced parkinsonism, including asymmetric presentation in six of them, resting tremor in five, and absence of dystonia (Jankovic, 2005). Such symptoms are more common in individuals with PD. In addition, there were some concerns expressed about the validity of the diagnosis of manganese-induced parkinsonism in these subjects and the lack of qualifications of the diagnosing physician in a subsequent letter to the editor (Chu, 2004). It is difficult to draw any conclusions regarding any association between Mn and neurological effects from this case series, and this study cannot be relied upon to make conclusions regarding Mn exposure and development of manganism, PD, or parkinsonism.

Josephs et al. (2005) reported the findings regarding eight welders referred to the Mayo Clinic with a variety of neurological complaints. The authors reported that all eight welders had "chronic and intense exposure to ambient welding fumes and reported inadequate ventilation or other safety measures." All of the welders performed MIG or TIG welding of stainless steel or galvanized steel. The reported symptoms included headaches, mood changes, transient double vision, memory loss, imbalance, tremor of head and hands, vertigo, slurred speech, myoclonic jerks, and reduced arm swing. Three of the cases were diagnosed with parkinsonism, although two of the three cases had asymmetric reduced arm swing, which is more characteristic of idiopathic PD. Serum Mn levels were elevated in 7 out of 8 welders (ranged from 0.8 to 1.3 ng/ml; normal was 0.4–0.85 ng/ml). The elevated levels returned to normal within a few months in three welders. All eight patients had bilateral hyperintense signals on T1-weighted MRI sequences in the globus pallidus in their initial

MRI scan. In the six welders with follow-up MRI head scans the MRI signal increased or remained unchanged in two welders that had continued exposure. Of the four welders who stopped welding, the MRI signal remained unchanged in one, decreased in two, and disappeared in another welder in subsequent MRIs. Six of the eight welders had normal CT scans. The response to L-dopa was partial in three patients, but reported to be less than typically occurs with PD. The authors concluded that these individuals displayed Mn-induced neurotoxicity, although they acknowledged that further investigation is necessary before such a conclusion can be made.

Kenangil et al. (2006) reported that a 32-year old welder developed Parkinsonism, severe postural instability, dystonia, and pyramidal signs during his 10th year of welding in a shipyard in Turkey. The neurological symptoms markedly worsened three years after he stopped welding. A T1-weighted MRI demonstrated symmetrical increased signals in the globus pallidus at the 4th months after his symptoms and he did not respond to treatment with dopaminergic agents. There was no information regarding exposure levels during welding.

Most of these cases apparently involved high exposures to substances in the workplace over long periods of time with little or no ventilation. It is not possible to attribute the observed neurological effects to a specific chemical or etiologic agent in these cases. These case reports indicate that these individuals exhibited a variety of neurological symptoms that may be due to several factors, including exposure to neurotoxic substances in the workplace or home environment, familial risk factors, other illnesses, or other unidentified etiologic agents. Despite these results, it is important to note that case reports are hypothesis-generating observations and do not provide evidence of causal association; however, the paucity of case reports suggests that there is no evidence of a significantly increased risk of developing clinical neurological symptoms, manganism, or early-onset PD from welding processes under normal conditions of exposure with some ventilation controls.

In summary, many of the studies conducted on welders included only self-reported neurological effects, lacked personal exposure or workplace TWA data and detail about Mn exposure sampling and/or ventilation, and/or had inadequate control groups, which may introduce bias into the results (Chandra et al., 1981; Anatovskaia 1984; Sjögren et al., 1990, 1996; Korczynski, 2000; Racette et al., 2001, 2005; Bowler et al., 2003, 2006a). All of these factors make it difficult to reach substantive conclusions as to whether welders are at risk of developing subclinical and/or clinical neurological effects, and it does not appear that any of the studies conducted to date provide compelling evidence that such a risk exists. Most of the studies on welders have significant methodological issues that need to be considered carefully when drawing conclusions regarding the risk of subclinical and/or clinical neurological effects in welders. The lack of quantitative information on exposure levels of Mn in the welding fume makes it difficult to establish a dose-response relationship or threshold for the reported neurological effects. With respect to the case reports of clinical neurological effects in welders, airborne Mn levels in most cases were likely excessive, as the affected welders had worked in railroad industries in which the Mn content of the welding rods was high (Nelson et al., 1993; Franek, 1994), in confined spaces with poor ventilation (Sadek et al., 2003; Koller et al., 2004), where workplace hygiene was poor (Rasmussen & Jepsen, 1987; Josephs et al., 2005) or where welding tasks were associated with an excessive risk of exposure (Discalzi et al., 2000). In addition to Mn exposure, risk factors that can influence the risk of neurological effects among welders include liver impairment, carbon monoxide poisoning, organic solvent exposure, exposure to other neurotoxic substances in welding fume, and brain accumulation of iron (Antonini et al., 2006). For example, it has been observed that a significant number of liver dysfunction patients exhibit moderate to severe parkinsonism (Burkhard et al., 2003; Nagatomo et al., 1999; Pal et al., 1999; Spahr et al., 1996), and it has been hypothesized that accumulation of iron in the brain may be associated with PD (Jellinger, 1999; Berg et al., 2001; Riederer et al., 2001).

DATA GAPS AND AREAS FOR FUTURE RESEARCH

Many critical data gaps regarding the risk of neurological effects associated with exposure to Mn remain, such as (1) identifying the most sensitive objective endpoint to detect early neurological effects in the workplace, (2) determining exposure levels associated with subclinical and clinical

effects, (3) understanding the shape of any dose-response curve that may exist, (4) evaluating differences in bioavailability for the various forms of Mn, (5) identifying the mechanism(s) of neurotoxicity involved, (6) addressing the existence of a subclinical to clinical continuum with increasing dose or duration of exposure, (7) determining whether clinical neurological effects progress once exposure ceases, and (8) evaluating whether cumulative Mn exposure produces adverse health effects. At this time, exposure to low levels of Mn in workplaces, such as those encountered during welding, has primarily been reported to be associated with subclinical neurological effects, many of which are subjective neurobehavioral symptoms that may be of questionable clinical significance. Questions also remain regarding the degree to which Mn is absorbed in the various chemical forms and oxidation states, how much is bioavailable once it is absorbed, and how it is distributed throughout the body. Some of these questions can be answered only through the use of animal models, while occupational cohort studies are necessary to address others. As described next, it is postulated that many of the aforementioned information gaps can be addressed by specific research efforts.

Characterization of Causal Relationship Between Welding and Neurotoxicity

There are several significant limitations in most of the welder studies that have been conducted, including (1) inadequate or faulty study designs, (2) a lack of or inadequate exposure data, (3) self-reported symptoms and/or exposures, (4) tests measuring subjective neurological effects, (5) lack of or inappropriate controls, and (6) confounding variables not adequately addressed. This makes it difficult to draw any conclusions regarding the risk of neurological effects as a result of welding. An evaluation of the case reports and cross-sectional studies suggests that there may be a relationship between welding and the occurrence of neurological effects in some welders, but it is difficult to confirm that exposure to an individual substance, such as Mn, in welding fume is the responsible etiologic agent. In addition, it is not possible to determine the actual Mn levels purportedly associated with neurological effects in welders from the available exposure information in these studies. A review of the studies of Mn-exposed cohorts revealed a lack of a defined dose-response relationship and a lack of progression of subclinical effects to clinically overt disease over time (Clewell et al., 2003). Because the welder studies are cross-sectional in design, the reported Mn exposures may not represent historical exposure levels. Further, there are other possible explanations for the reported neurological effects that need to be considered, including other exposures (motor or chemical), reporting bias, lifestyle factors, and familial history. There have been large retrospective cohort studies to compare the rates of neurological conditions in welders versus the general population or nonwelders (Fryzek et al., 2005; Fored et al., 2006). The findings from these studies did not support a relationship between welding and PD or other neurological disorders. However, a well-designed prospective epidemiological cohort study of welders should be conducted to determine whether there is an increased risk of developing clinically significant neurological effects and/or manganism and to establish incidence and prevalence rates for clearly defined objective neurological conditions.

Characterization of Welder Exposure to Mn

It is important to have a complete understanding of the extremely wide range of potential exposures produced by various welding technologies to determine whether welders are actually exposed to elevated levels of Mn in the fume. The process of melting the parent metal and the consumable produces concentrated particulate fumes and gases.[14] The aerosols that form during welding are complex and evolve from a variety of dynamic processes such as nucleation, condensation, and coagulation (Zimmer & Biswas, 2001; Zimmer, 2002). Depending on the metallurgy of the filler wire, fluxing compounds, and base metal, the aerosols that are produced from a welding process may be composed of individual spherical particles, although it is more likely that these processes

[14]In addition to the generation of fumes and gases, the welding process generates variable amounts of ultraviolet, visual, and infrared radiation (Burgess, 1991; Sferlazza & Beckett, 1991; Beckett, 1996). There is also frequently spatter of hot metal and slag particles during the welding process (Palmer & Eaton, 2001). These molten, spattered particles may also contribute to a small fraction of the composition of the welding fume. Other by-products of welding include heat, electrical current, noise, and vibration.

TABLE 4. Welder Cross-Sectional and Exposure Studies Reporting Mn Levels

Study	Mn Range (mg/m^3)	Sample Type	Location
Chandra et al. 1981	0.44–2.6	Mn samples in the "air in the breathing zone"	India
Siegl and Bergert 1982	1–4	Concentrations in "the breathing air at stationary work places"	Germany
Järvisalo et al. 1992	0.08–0.69	Mean airborne Mn in "breathing zone"	Finland
Karlsen et al. 1996	ND–0.015 (mean: 0.004)	Mn content in fumes in "breathing zone"	Norway
Sjögren et al. 1996	0.1, 0.9	Two TWAs; no other information	Sweden
Yim et al. 1998	0.03–1.15	Area samples at 12 locations in 3 departments	Korea
Jin et al. 1999	(0.005–1.7) (mean: 0.14)	Mn fume – area samples of shielded metal arc welding	Korea
	range, 0.005–9.27 (mean: 2.1)	Mn fume – area samples in CO_2 arc welding	Korea
Moon et al. 1999	0.15 (arithmetic mean)	Mn fume – personal samples	Korea
Korczynski 2000	0.01–4.93 (mean = 0.5)	Mn fume – personal samples	Canada
Luse et al. 2000	0.003–2.6	Mn in the "air of work environment"	Latvia
Smargiassi et al. 2000	0.002–0.3 (mean = 0.12)	Respirable Mn – personal samples	Canada
Susi et al. 2000	0.0005–1.31 (mean = 0.2)	61 personal samples in 1995	Canada
	0.001–0.47 (mean = 0.07)	75 personal samples in 1996	
Sińczuk-Walczak et al. 2001	0.04–2.67 (mean = 0.4)	Mn – personal samples	Poland
Li et al. 2004	1.45	Airborne Mn levels in breathing zones	China
Lu et al. 2005	0.2–1.5	Mn – area samples taken in the breathing zone	China
Halatek et al. 2005	0.003–3.37	Mn – personal samples	Poland
Harris et al. 2005	0.16–1.0	Respirable Mn inside helmet	U.S.
Cole et al. 2007	<0.001–0.32	Mn outside helmet	U.S.
	<0.001–0.25	Mn inside helmet	

Note: TWA = time-weighted average; ND = non-detect.

form complex agglomerates (Zimmer, 2002). These agglomerates are composed of tens to thousands of individual particles with agglomerate sizes predominantly from 0.1 to 10 μm. In contrast, the individual particles that make up these agglomerates typically range from 0.01 to 0.1 μm.

Some studies measured the levels of Mn in welding fumes generated during various types of welding, as shown in Table 4 (Chandra et al., 1981; Siegl & Bergert, 1982; Kura & Mookoni, 1998; Sjögren et al., 1996; Korczynski, 2000; Luse et al., 2000; Järvisalo et al., 1992; Moon et al., 1999; Smargiassi et al., 2000; Li et al., 2004; Cole et al., 2007). Most of these studies report levels ranging from 0.001 to 4.93 mg/m^3, below the current OSHA PEL of 5 mg/m^3. However, many of the exposure data reported in these studies have limitations, with information lacking concerning: (1) duration and frequency of exposure measurements; (2) sample location (area vs. personal); (3) particle size; (4) form of Mn; and (5) ventilation. During the welding process, the Mn content may be the highest directly over the smoke plume, but with appropriate ventilation and personal protection, the welder is typically exposed to much lower levels of Mn; therefore, it is important to measure appropriate locations to understand the quantity of respirable Mn to which welders may be exposed. A carefully designed dose reconstruction or exposure simulation study would be useful to determine the range of exposures that a welder may experience. This will likely involve: (1) sampling in the breathing zone during several different activities using different welding technologies to evaluate fumes from a range of Mn-containing welding electrodes and materials, (2) assessing exposure levels under typical and worst-case conditions, and (3) determining the specific form of Mn and size of particulates in the welding fume. It is also important to measure levels generated during the most common types of welding activities currently in practice, such as mild steel welding.

A study was conducted by Harris et al. (2005) to obtain exposure levels of total fume, total Mn, and respirable Mn during welding in a confined space, where the variable that was adjusted was ventilation/dilution. Welder exposures (personal, area, inside helmet, outside helmet) were evaluated during different ventilation rates and compared findings were compared to current and past occupational guidelines. They compared the sampling data to AGGIH's TLV-TWA guideline of

0.2 mg/m^3, as well as the 0.03-mg/m^3 draft guideline that was vacated by ACGIH in 2004. The authors used the 0.03-mg/m^3 guideline for respirable Mn, as they stated that this was the value in place when they conducted this study. Three electrodes were evaluated that were described as those frequently used for cladding carbon steels, with Mn content in the flux ranging from 1.4 to 5.4% for 2 electrodes (E6010 and E7018) and 48% for 1 electrode (Mangjet). They collected personal samples, including inside helmet (total and respirable Mn), outside helmet (total fume only), upstream/downstream of welder (total and respirable Mn), and area samples. Samples were collected for 60 min for 2 electrodes and for 30 min for the high-Mn Mangjet electrode. The ventilation rates in the room ranged from 0 to 2000 cubic feet per minute (cfm). For 2000 cfm (56.63 m^3/min, industry standard according to the article), samples inside helmet were $<$0.2 mg/m^3 for total and respirable Mn for two electrodes. The area samples upstream and downstream of the welder exceeded the 0.2 mg/m^3 TLV for the 2 electrodes (0.34 and 0.37 mg/m^3). For the Mangjet electrode, all results were $>$0.2 mg/m^3 for total and respirable Mn (range, 1.0–1.7 mg/m^3). The Mn concentrations increased as ventilation rate decreased and the concentrations upstream/downstream from the welder were higher than those in the helmet. One problem with this study design is that the exhaust was being pulled from knee-height and the investigators did not circulate the air at breathing height (or hot plume height), which would typically be the case in a workplace. Further, it is important to note that it is not appropriate to compare the 1-h sampling period to the 8-h TWA, unless the worker is continuously welding throughout an 8-h shift.

Clearly, a multitude of potential exposure scenarios must be considered when designing a study to measure Mn exposure levels in welders due to the number of metals, fumes, gases, and other substances that arise from the process itself. It should be noted that changes in welding processes over time could also affect overall exposure. A general reduction in welding exposures over time due to process modifications is likely not the only factor affecting exposure. Differences in welding technique, composition of consumables, variety of base metals used, measurement techniques, and implementation of ventilation also likely play roles. For example, Hewitt (2001) evaluated the exposure from total welding fumes from the 1960s to the 1990s in Russian shipbuilding, reporting a decrease in exposure of two orders of magnitude over a 30-yr period. These issues must all be investigated and understood when evaluating the exposure of workers to Mn during welding.

Mn Dose-Response Relationships

Data concerning dose-response relationships in so-called "high-exposure" industries where the majority of the clinical cases of manganism were observed were practically nonexistent until the late 1980s and early 1990s. Several studies during the last two decades report dose-response relationships and/or estimated thresholds for neurological effects in workers exposed to Mn (and often other compounds) in settings such as smelters, dry alkaline battery manufacturing facilities, and ferromanganese alloy production plants (Roels et al., 1987a, 1992; Iregren, 1990; Hua & Huang, 1991; Chia et al., 1993a, 1993b; Kaji et al., 1993; Mergler et al., 1994; Lucchini et al., 1995, 1997; Gibbs et al., 1999). Of the aforementioned studies, the study by Gibbs et al. (1999) on 75 workers in an electrolytic Mn metal-producing plant is perhaps the most informative in terms of dose-response interpretation, because it (1) examined a well-defined exposed population with apparently little or no mixed exposure to other neurotoxicants; (2) had a well-matched control group by age, gender, race, and pay grade; (3) used well-established and relatively objective measures of neurological deficits (as opposed to self-reported symptoms); (4) reported air data in terms of TWA respirable fractions; and perhaps most importantly, (5) reported individual exposure data and response information for each individual worker (Finley & Santamaria, 2005). It should be noted that Gibbs et al. (1999) examined relatively low exposure conditions, with mean airborne respirable levels of only 0.066 mg/m^3 (compared to mean airborne levels of 0.12 mg/m^3 and greater in other studies), and did not find an increased incidence of neurobehavioral effects in the Mn-exposed workers (Finley & Santamaria, 2005). The median exposure level in this study for respirable dust (0.051 mg/m^3) is higher than the lowest level of respirable dust (0.032 mg/m^3) reported by Mergler et al. (1994) at which subclinical neurological effects were observed. The Roels et al. (1992) study, which reported increased neurobehavioral deficits in 92 workers in a dry alkaline battery

plant exposed to mean airborne respirable levels of 0.3 mg Mn/m^3, also has the methodological attributes just described; however, Roels et al. (1992) examined fewer endpoints (three measures of psychomotor function, compared to five measured by Gibbs et al., 1999), and the response data were reported in quantal terms, rather than continuous, which limits the information that can be obtained from dose-response modeling.

Clewell et al. (2003) published a comprehensive benchmark dose analysis of the Roels et al. (1992) and Gibbs et al. (1999) data, in which the individual response results were interpreted in conjunction with the TWA personal air measurements using a variety of dose-response models. The results suggest that chronic exposure to airborne respirable levels up to approximately 0.1–0.3 mg Mn/m^3 as an 8-h TWA should pose little to no risk of developing subclinical signs of neurobehavioral effects; however, there are no data for welders that can be used to establish a dose-response relationship for Mn exposure during welding and subclinical or clinical neurological effects. Most of the studies that were conducted with welders did not report individual personal measurements for Mn, which are necessary for elucidating an exposure-response relationship.

Bioavailability of Different Forms of Mn

Several questions remain about how much Mn may actually be absorbed and penetrate the blood–brain barrier in workers exposed to various chemical and physical forms of Mn (dust, Mn oxides, welding fume). Significant differences in the dose of Mn that may cross the blood–brain barrier and be available for toxicity are likely for different forms and particles sizes of Mn that may be generated by different occupational activities (Jankovic, 2005). In contrast to relatively low concentrations of Mn in the welding fumes in the breathing zone of the welder, particles found in dust generated in mining and ore crushing operations contain a much higher concentration of Mn, potentially leading to a higher accumulation of Mn in the body. Further, fumes during welding are formed by the vaporization of metals under conditions of extreme heat and the subsequent condensation with iron results in a tightly bound, nonsoluble FeMn amalgam, making the translocation of any free Mn from the lungs to the bloodstream and then across the blood–brain barrier more difficult (Jankovic, 2005). Issues regarding onset of disease and exposure, as well as differences in dissolution rates of Mn in various body compartments (e.g., alveolar macrophages vs. lung tissue), must be considered. More studies are necessary to evaluate the bioavailability and potential toxicokinetics of Mn after the inhalation of welding fumes.

Biomarkers of Mn Exposure and/or Effect

Many studies were conducted in Mn-exposed cohorts to determine whether the detection of Mn in biological tissues or fluids can serve as biomarkers to predict past or current exposure levels and/or the potential for adverse health effects (e.g., levels in blood [MnB] or urine [MnU]). Other studies have been conducted to evaluate the relationship between Mn exposure and high signal intensities on T1-weighted brain MRIs and whether such findings can serve as biomarkers of exposure and/or effect for Mn (Dietz et al., 2001; Kim, 2004; Kim et al., 2005; Pal et al., 1999; Nelson et al., 1993). However, the clinical significance of elevated signals detected on MRIs is not established, making it difficult to use such data as biomarkers of effect. In addition, the elevated intensities are not necessarily evidence of Mn exposure, as other factors may cause increased intensities on MRIs.

Because Mn can be measured directly in blood, serum, cerebrospinal fluid, feces, or hair, it has been used as a biomarker of exposure in occupational studies; however, the usefulness of a biomarker of exposure depends on how accurately it reflects the environmental exposure level, which typically requires studies to validate the biomarker. Studies attempted to use Mn biomarkers as a measure of cumulative exposure (Tsalev et al., 1977) or to correlate with subclinical or clinical neurological effects (Chandra et al., 1981; Roels et al., 1987b, 1992; Sjögren et al., 1996; Kaji et al., 1993; Lucchinni et al., 1999; Mergler et al., 1999; Luse et al., 2000). These studies are often difficult to interpret in terms of prior Mn exposure, due to the fact that Mn is a normal dietary component and is present in all human tissues and fluids, so baseline levels must be considered when evaluating studies involving use of biomarkers of exposure. A variety of potentially confounding

factors also must be considered when evaluating any reported correlations between Mn biomarkers and exposure levels. For example, some studies showed that Mn levels in human tissues and body fluids may be altered in various disease states (Saric, 1986). Specific early biomarkers of effect, such as subclinical neurobehavioral or neurological changes, have not been established or validated for Mn. Although some studies suggested that some genes may serve as susceptibility biomarkers for Mn neurotoxicity, there are currently no validated biomarkers of susceptibility (Smargiassi & Mutti, 1999; Zheng et al., 1999).

The usefulness of biomarkers for assessing past exposures to Mn is debatable. Blood and urine Mn levels have been the most widely used biomarkers of exposure in occupational studies. Although Mn levels in hair were also evaluated in a few studies, hair is not a reliable indicator of exposure or internal dose, because there is potential for external Mn exposures that may affect Mn levels in hair. The concentration of Mn in hair may also be affected by the degree of pigmentation (Pal et al., 1999). Blood Mn is not a good indicator of the amount of Mn absorbed shortly before sampling or during the preceding days, because it changes very little with Mn exposure by inhalation (Smargiassi & Mutti, 1999). Blood Mn may also be influenced and change as a result of dietary intake, which may also confound study results. There is also a lot of inter- and intra-individual variability in MnB levels, making it a more useful parameter to evaluate external exposure on the population level than on the individual level. Urinary Mn excretion is not a good indicator of Mn exposure, because Mn is excreted primarily in the bile, and only approximately 1% is excreted in urine (Saric, 1986). Mn has a half-life in blood of 10 to 42 d (Nelson et al., 1993) and a half-life of less than 30 h in urine (Roels et al., 1987b). These relatively brief half-lives make MnB or MnU more indicative of recent exposure, rather than serving as a marker of long-term or chronic exposure. In general, MnB was used as an indicator of the past few weeks of exposure, generally less than 1 mo (Lander et al., 1999). MnU may indicate exposure within the past day or two.

Several variables may affect the concentration and pharmacokinetics of Mn in the blood and urine. With the exception of individuals with liver disease, excess Mn is usually removed from the body within several days, making it difficult to measure past exposure. There are specific deposits of Mn in the body from which elimination takes place over a prolonged period of time, in the following order of elimination: lungs, kidneys, liver, intestine, heart, bones, and brain (Whitlock et al., 1966). In addition, the chemical form of Mn determines the biological half-life, with compounds such as MnO_2 being eliminated in 2–3 mo, while elimination time is shorter for more soluble compounds, such as Mn sulfate and Mn chloride found in Mn salt-producing plants (Lucchini et al., 1995).

Studies of Mn-exposed workers have not been able to detect correlations between blood or urine levels and neurological measures. Most studies evaluated nonwelder cohorts (Kaji et al., 1993; Smyth et al., 1973; Kim et al., 1994, 1999, Deschamps et al., 2001), while others reported an association, typically on a group level rather than on the individual level (Lucchini et al., 1995; Mergler et al., 1994; Roels et al., 1987b, 1992; Luse et al., 2000). A few studies in welders, however, found that Mn-exposed workers excreted more Mn in urine and/or had higher blood Mn levels as a group than unexposed control subjects (Järvisalo et al., 1992; Chandra et al., 1981; Luse et al., 2000; Lu et al., 2005; Ellingsent et al., 2006). Järvisalo et al. (1992) conducted biological monitoring in MMA/MS welders, reporting that individual differences were great and that measurement of Mn in blood or urine may be useful only for monitoring Mn exposure at the group level. The authors reported that blood and urine Mn levels were higher in welders than in unexposed controls; however, the levels were not significantly different and urinary Mn excretion was not correlated with levels of Mn or duration of exposure. Chandra et al. (1981) reported that welders from 3 plants with Mn levels ranging from 0.44 to 2.6 mg/m^3 had higher MnU levels than control subjects who were not exposed to Mn, and that the serum levels were too variable to be considered of diagnostic significance. They also reported that because the welders had higher MnU levels than controls and also had more self-reported neurological symptoms, elevated MnU may serve as a biomarker of effect.

Luse et al. (2000) reported elevated MnB and Mn in the hair of welders and some neurobehavioral effects in welders exposed to 0.003 to 2.6 mg/m^3 Mn compared to control subjects. They reported that the welders had significantly higher levels of Mn in blood and hair than the control

group: 7.6 and 3.2 times higher, respectively. Another group of welders exposed to Mn did not have higher Mn levels in blood than the controls, and the MnB or MnU levels were not correlated with the reported decreases in motor function (Sjögren et al., 1996). The studies that detected elevated MnB and or MnU levels in groups of workers with subclinical neurological symptoms have not identified a dose response to correlate the biomarker with effects, so it is difficult to interpret the clinical significance of the reported MnB or MnU levels.

Increased knowledge of the toxicokinetics of Mn would improve the understanding between external exposure parameters, biological measures, and neurological outcomes. The blood and brain Mn level associated with neurological effects is not known. Because the relationship between external and internal measures of Mn has not been clearly elucidated, studies attempt to correlate Mn biomarkers (i.e., Mn in blood, urine, and hair) with external Mn exposure levels in the hope of discerning relationships between exposure and biological levels (Roels et al., 1987b, 1997; Järvisalo et al., 1992; Wennberg et al., 1991; Chia et al., 1993; Mergler et al., 1994; Lucchini et al., 1995). In addition, there is a lack of consistency or dose-response relationship between internal or external measures of Mn exposure and neurobehavioral outcomes (Mergler & Baldwin, 1997). Lander et al. (1999) reported that although there are no biological limit values for Mn in blood, subclinical intoxication was observed in workers with moderate (1 to 4 μg/L) increases in MnB above control groups (Lucchini et al., 1995; Mergler et al., 1994; Roels et al., 1992). In a community-based study of blood Mn and neurotoxicity, Mergler et al. (1999) suggested that blood levels as low as 7.5 μg/L may be associated with neurological dysfunction; however, this is within the normal range of blood Mn levels (7–12 μg/L), which casts some doubt on the clinical significance of this MnB level (Oberdörster & Cherian, 1988; Beuter et al., 2004). Thus, a dose-response relationship for Mn exposure and neurotoxicity remains elusive, even in the presence of biological data.

CONCLUSION

Toxicological studies, case reports, and epidemiological studies on the neurological effects of Mn exposure were conducted and reported in the scientific and medical literature over the last 100 yr in a variety of industries. There is no doubt that Mn is a neurotoxic substance at certain exposure levels; however, the critical question regarding what levels are associated with neurological effects remains unanswered. The available toxicological and epidemiological data are insufficient to determine a dose-response relationship for subclinical or clinical neurotoxicity and exposure to Mn. While biological measurements of Mn in blood and urine may have some utility in assessing whether recent exposure has occurred, the current evidence suggests that the pharmacokinetics of inhaled Mn is not understood sufficiently to justify the development of a predictive model for past or current exposures or to predict neurological effects based on biological data. Further research is needed to develop validated biomarkers of exposure, effect, and susceptibility for Mn and to elucidate their biological and clinical significance. In addition, it is imperative that a clear understanding of the toxicokinetics be developed for the diverse forms of Mn that workers may be exposed to in various occupational settings. Such information will contribute to understanding the differences in neurotoxicity observed in workers from the various occupational settings involving exposure to Mn.

Welding is an occupation that involves highly diverse processes and environments resulting in mixed exposures to numerous chemicals; therefore, the available studies of welders should be interpreted with caution. The weight of evidence to date is not sufficient to conclude that welders are at an increased risk of neurotoxicity from exposure to Mn during the welding process. The Mn levels that have been reported in several studies of welders are typically fairly low, and are usually below the current OSHA PEL of 5 mg/m^3. A welder exposed to fume containing a high Mn content, and working in a confined space with inadequate ventilation for a long period of time, might inhale enough Mn to produce clinical symptoms of neurotoxicity; however, with the exception of approximately 15 case reports, a review of the medical and scientific literature does not reveal any reliable association between welding and clinical neurological effects, manganism, or PD. There are no data from welder studies that can be used to establish a dose-response relationship for Mn, because very few studies report exposure measurements and symptoms for individual welders. Although most of

the welder studies suffer from significant limitations, thereby complicating the ability to draw conclusions with regard to risk of developing neurological effects as a result of welding, the weight of evidence does not confirm that exposure to Mn in welding fumes is the responsible etiologic agent. Areas of investigation to further evaluate any association between exposure to Mn and neurotoxicity should include (1) whether or not subclinical effects proceed to clinical effects in the absence of additional Mn exposure (long-term follow-up of Mn-exposed cohorts), (2) whether there is a mechanistic basis for Mn as a risk factor for PD (i.e., animal studies), and (3) development of a standard suite of objective, diagnostic criteria for evaluating the subclinical effects of Mn exposure in humans (Finley & Santamaria, 2005).

No sound epidemiological study exists that shows an association between welding or welding fume and PD, and there are no reliable data to support that welding fumes can accelerate the onset of PD. On the contrary, valid studies that describe exposure levels and/or health effects in welders demonstrate that no such association is present. The fact that an increased incidence of PD has not been reported in Mn miners and smelter workers suggests that an increased incidence of this disease in welders is unlikely, because welders are exposed to much lower levels than miners and other cohorts. In conclusion, with the exception of a few case reports of neurotoxicity in welders, there is an absence of reliable exposure and epidemiology studies to support a causal association between clinical neurotoxicity and exposure to Mn during welding.

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