**EXPERT REPORT OF**

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**IN THE MATTER OF**

**WELDING ROD PRODUCTS LIABILITY LITIGATION**

**IN THE**

**UNITED STATES DISTRICT COURT**

**NORTHERN DISTRICT OF** [redacted]

**EASTERN DIVISION**

**CASE No.** [redacted]

**MDL DOCKET** [redacted]

**JUDGE O'MALLEY**

**CONSULTOX, LIMITED**

**DAMARISCOTTA, MAINE**

**SEPTEMBER 1, 2004**

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## QUALIFICATIONS

I, Richard A. Parent, PhD, DABT, FATS, RAC, ERT, am a board certified toxicologist with over 15 years' experience in the field of industrial toxicology and an additional 20 years' experience in litigation support for both the plaintiff and defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984, I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in various products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as for the defense. I have served as a consultant to the American Welding Society from 1982 to 1986 and in that capacity have designed studies to assess the toxicity of fumes resulting from the welding process. I am board certified by the American Board of Toxicology, the Academy of Toxicological Sciences, and the Regulatory Affairs Professional Society. I am a recognized expert in toxicology in France and the European community. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Appendix A and a listing of my testimony in past depositions and trials for the past four years in Appendix B.

## MATERIALS REVIEWED

- Open literature citations as identified in Appendix C
- Deposition of Brian Buckley, PhD, taken on July 22, 2004
- Deposition of Barry S. Levy, MD, MPH, taken on July 2, 2004
- Deposition of David Garabrant, MD, MPH, taken on July 21, 2004
- Deposition of William E. Longo, PhD, taken on July 14, 2004
- Deposition of Kenneth Reuhl, PhD, taken on July 23, 2004
- Deposition of William M. Ewing, CIH, taken on June 25, 2004
- Deposition of Paul A. Nausieda, MD, taken on June 17, 2004
- Depositions of Charles Warren Olanow, MD, taken on August 3 and 12, 2004
- American Welding Society, "Effects of Welding on Health", Franklin Institute Report 1978 (see Appendix D)
- "Welding Fume Report" by MAS of Suwanee, GA, dated April 29, 2004
- The National Shipbuilding Research Program, Welding Fume Study; Final Report; US Dept. of the Navy, by DynCorp, BHS, Environmental Health & Safety Services, January 28, 1999
- Various literature and industry publications as partially indicated in the timeline found in Appendix D

## INTRODUCTION

"Welding is the process of joining metals by electric arc or flame with a filler material. The filler material, also called the consumable, is usually a coated electrode or wire that contributes metal to the joint. The four most common welds are tungsten inert gas (TIG), metal inert gas (MIG), metal active gas (MAG), and manual metal arc (MMA)."[1] The consumable produces 80-90% of the fume released in this process, and manganese (Mn) is a component of that fume.

Manganese is a very hard metal used to increase the strength of steel alloys.[2] It is a naturally-occurring element that is found in rock, soil, water, and food, and is a normal component of the human body.[3] It also is an essential element for the human body,[4,5] essential for brain development[6] and metabolism as well as for defense against oxidative injury.[6] Manganese is a cofactor for the antioxidant enzyme mitochondrial superoxide dismuthase,[7] and other enzymes as well.[2] Normal intake of manganese mostly through the human diet is estimated to be 1 to 9 mg per day,[2,3] and its half-life of elimination from blood ranges from 10-42 days.[8] About 98% of the metal is excreted in the bile after being cleared from the blood by the liver.[5] Manganese can be absorbed into general circulation through the gastrointestinal tract or through the lungs.[2,5]

The toxicity of manganese has been reported as early as 1837[9] as indicated in Appendix D. "There is conclusive evidence from studies in humans that inhalation exposure to high levels of manganese compounds (usually $MnO_2$, but also including $Mn^{+2}$ and $Mn^{+3}$) can lead to a disabling syndrome of neurological effects sometimes referred to as 'manganism' ".[10] Some believe that there are three stages of manganese neurotoxicity: 1) behavioral changes, 2) parkinsonism features, and 3) dystonia with severe gait disturbances.[11] "Manganese intoxication is a well-known cause of parkinsonism and dementia."[12] A 1934 publication states, "The clinical course and symptomatology of the rare industrial disease due to inhalation and ingestion of dusts containing manganese are now well known",[13] and an earlier 1932 publication states, "Chronic manganese poisoning is a disease which at present time is easily recognized . . .".[14]

This report presents appropriate regulatory and scientific literature describing the nature of welding fumes with particular emphasis on manganese, the generation of welding fumes, the quantification of manganese in welding fumes using different welding rods, and the health effects of inhaling welding fumes, including parkinsonism. Several exposure modes and occupations involving manganese exposure and toxicity are addressed since the basal ganglial region of the brain is the target organ of manganese intoxication independent of the mode of exposure or route of entry into the body. As will become clear in this report, "manganism", "parkinsonism", and "Parkinson's Disease" cannot be adequately defined as separate entities since they all result from various influences on a genetic template containing at least 12 different loci for mutations which have been linked to this disease syndrome.[15] Recent perspectives on this subject favor a continuum of diseases related to parkinsonism with various disease presentations being labeled as "primarily genetic" or "primarily

environmental".[15] "Instead of looking at Parkinson's Disease as a single disease, we can regard it as a syndrome with many causes that may be genetic or environmental".[15] In this report the focus is on parkinsonism of "primarily environmental" origin with the offending agent being manganese. In describing the effects of manganese-containing welding fumes on the central nervous system, a recent industry-sponsored study stated, ". . . some permanent brain damage can result [ed. note: from welding fumes] and symptoms are identical to Parkinson's Disease" (see "Materials Reviewed" Section, National Shipbuilding Research Program). These discussions are followed by a formal causation analysis addressing the potential for a causal relationship between manganese exposure and the development of parkinsonism using the Hill criteria.[16]

## REGULATORY ASPECTS OF MANGANESE

Although the Occupational Safety and Health Administration (OSHA) has a permissible airborne exposure limit (PEL) of 5 mg/m$^3$ as Mn (8-hour time-weighted average or TWA), and the National Institute of Occupational Safety and Health (NIOSH) recommends a PEL of 1 mg/m$^3$ (10-hour TWA),[17] the American Conference of Governmental Industrial Hygienists (ACGIH) has suggested a threshold limit value (TLV) of 0.2 mg/m$^3$ and lower as Mn.[5,17-20] There is ample support in the literature for the lower level of exposure as recommended by the ACGIH.[21-28] Neurobehavioral tests to identify early signs of manganese intoxication in workers exposed to a median concentration of as little as 0.14 mg/m$^3$ manganese have been positive,[25] an observation supported by others who have reported neurological effects at 1 mg/m$^3$ manganese.[28] One study of 60 workers in two Swedish foundries where men were exposed consistently to 0.25 mg/m$^3$ for 17-18 years reported inferior performance in simple reaction time.[25,29] Another study based on WHO Neurobehavioral Core Test Battery administered to 17 manganese-exposed workers exposed to a mean concentration of 1.59 mg/m$^3$ manganese from 1981 to 1991 reported neurological deficits.[30] Finally, the US EPA calculated a reference airborne concentration (Rfc) of manganese that would not produce adverse health effects in man based on a lowest adverse effect level of 150 µg/m$^3$ manganese and an uncertainty factor of 100. The Rfc calculated was 0.05 µgMn/m$^3$[32] A recent industry-sponsored study states, "Current shipyard practices place little emphasis on controlling employee exposures to welding fumes"(see "Materials Reviewed" Section of this report, National Shipbuilding Research Program).

## EXPOSURE TO WELDING FUMES AND GASES

The welding environment involves exposure to manganese and other heavy metals but also involves exposure to gases which can have a significant influence on the ability of the lungs to protect against and clear these heavy metal oxide particulates, including manganese compounds. Ozone and nitrogen oxides are gases produced by the welding process, and they have a profound effect on the ability of the lungs to clear particulates, including manganese produced by the welding process via the mucociliary escalator.[31-36]

Welding fumes are cytotoxic to macrophages which also are involved in clearing particulates from the lungs.[37-41] As a result of these actions by welding fumes, welders have been reported to experience decrements in total lung capacity with bronchitis and asthma,[42] pulmonary function deficits,[43-45] chronic bronchitis,[5,46] pulmonary fibrosis,[47,48] and even lung cancer.[49]

Manganese alone has been reported to cause inflammatory responses in the lungs, including pneumonitis, cough, bronchitis, COPD, and decreased lung function.[5] The effect of these various detrimental processes on the lungs is that the manganese which is inhaled in welding fumes is not readily cleared because of a compromised pulmonary defense capability. It remains in the lungs as a result and is slowly absorbed into systemic circulation. It finds its way to and accumulates in the brain as has been demonstrated by experiments in primates[50-54] and other animal models.[55-57] In addition, manganese has been found to have a unique capacity to be taken up via the olfactory pathway and pass transneurally to other parts of the brain in rats.[56-58]

## MANGANESE IN WELDING FUMES

There are numerous reports about manganese in welding fumes including those published by the American Welding Society (See Appendix D) and those cited in the "Materials Reviewed" Section of this report. "Steel-alloy welding is perhaps the greatest source of industrial exposure to manganese".[19] Welding of soft steel is reported to involve high concentrations of manganese in the fumes[5] with one report describing a concentration of 10.23% manganese in manual metal arc (MMA) fumes and 7.0% in metal inert gas (MIG) fumes.[59] Another report found 6.2% manganese in MMA/mild steel fumes and 1.5% in MIG/stainless steel fumes[60] and MMA fumes being produced at a rate of 0.262 mg/m$^3$ containing 8.12% manganese.[61] Other reports found that electric arc welding produced concentrations from 0.2 to 3.3 mg/m$^3$ in air,[62] that welding with common neutral electrodes produced fumes containing up to 21.7% manganese, that deep penetration high yield electrodes yielded manganous oxide concentrations up to 24.7% in welding fumes, and that electrodes with acid coating yielded fumes containing up to 15.2% manganese.[63]

Specific welding rods have been reported to generate varying amounts of manganese in the fumes. One study of fumes generated from several types of welding rods from different manufacturers reported the following findings of airborne manganese: E6011 (0.20-0.30 mg/m$^3$ manganese); E6014 (0.11-0.26 mg/m$^3$); E6013 (0.20-0.39 mg/m$^3$); E6024 (0.23-0.37 mg/m$^3$); E318/16 (0.28 mg/m$^3$); E7016 (0.12-0.35 mg/m$^3$); E7018 (0.14-0.16 mg/m$^3$); E7024 (0.22-0.83 mg/m$^3$); and others.[64] Another study reported 2.7% manganese in MMA welding fumes using coated electrodes on stainless steel, 7% manganese from MIG welding of stainless steel plate, and 10.4% manganese in fumes from MIG welding of stainless steel plate.[65] The American Welding Society[66] reported the following concentrations of manganese in welding fumes from various welding rods: E6010, 4.0%; E7018, 4.6%; E70S-3, 7.8%; E70T-1, 11.1%; E308-16, 6.2%. Another

report described E6000 electrode for mild steel that contained from 0.4-0.6% manganese and coatings for E6020 and E6030 that contained from 10-25% manganese dioxide resulting in typical fumes containing about 2.8% manganese dioxide.[67] Fume generation rates during shielded metal arc (SMA) welding have been reported for various welding rods including E7018 (0.28-0.65 g/min), E7024 (0.29-0.68 g/min), and E308-18 (0.25-0.51 g/min).[68] Welding fume particulates, including manganese, are in the particle size range of 0.3 to 0.5 μm (micrometers),[65] putting them in the respirable range thereby allowing the deposition of the particulates into the deep lung. The American Welding Society has measured particle size ranges of some of the particulates from specific welding rods, including E6010 (0.09-0.54 μm), E70s (0.06-0.30 μm), and E308-16 (0.06-0.27 μm).[66]

## EXPOSURE TO MANGANESE IN WELDING FUMES

The dangers of inhaling welding fumes have been known to the welding industry for some time as noted in this 1944 US Naval Medical Bulletin: "There are health hazards connected with electric arc welding from breathing the fumes and gases generated". These hazards should not be minimized."[69] The need for adequate ventilation during these processes are noted in this quote from 1964: "Where toxic materials are involved or where natural ventilation is inadequate, it will be necessary to use mechanical ventilation in the form of local exhaust placed near the point at which the work is performed".[70] Indeed, the hazards of inhalation exposure to manganese in welding fumes have been known to the medical and scientific communities and the welding industry for some time.[14,71-94] Some of these earlier publications may be found in Appendix D of this report.

As recently as 1985 there is a report of gas shielded welding using electrode wire in a confined space with no suction resulting in a measurement of 68 mg/m$^3$ welding fumes in the breathing zone of a welder.[45] Another situation involved MMA welding in a shop with no direct suction resulting in a manganese concentration of 2.5 mg/m$^3$ in the breathing zone.[45] Other reports of actual measurements of fumes in occupational settings included exposures in a large room without the use of local exhaust ventilation resulting in concentrations of welding fumes in the breathing zone of 1.3-13.2 mg/m$^3$ for MMA welding, 0.9-12.9 mg/m$^3$ for MIG/MAG welding, and 0.8-4.2 mg/m$^3$ for TIG welding.[95] Concentrations of manganese in welding fumes in a shipyard are reported to be from 0.03 to 1.74 mg/m$^3$ in open areas and 0.02 to 0.79 mg/m$^3$ in confined spaces.[96] One study involving the use of welding rods and sticks containing from 11 to 25% manganese reported measurement from 3 to 4.6 mg/m$^3$ inside of the welding mask,[18] while another study reported the geometric mean and range of ambient manganese concentrations in welders and welding rod manufacture as being 0.53 mg/m$^3$ (0.1-1.56) and 0.15 mg/m$^3$, (0.02-0.42) respectively.[97] Another study demonstrated manganese levels that were five times that of non-exposed individuals based on 254 shipyard welders versus 237 controls,[98] while yet another study of 228 welders also demonstrated elevated manganese levels in hair samples.[99] Cutting of steel containing

17% manganese produces dust containing 25% manganese oxides and those fumes in the breathing zone may reach 40-70 mg/m$^3$ according to a Russian publication,[100] and a recent study of wire welding produced exposures up to 14 mg/m$^3$ during the welding process.[101] Additional data on manganese exposure during the welding process may be found in the "Welding Fume Report" cited in the "Materials Reviewed" section of this report.

## NEUROTOXICITY AND MANGANESE IN WELDING FUMES

A recent publication relating to the neuropsychiatric effects of manganese states, "Manganese intoxication is a well-known cause of parkinsonism and dementia".[12] One study of 60 welders from three plants involved with welding of stainless steel and mild steel reported neurological signs in 10/20, 5/20, 9/20 welders in each of the three plants with corresponding breathing zone levels of manganese being 0.44-0.99 mg/m$^3$, 0.5-0.8 mg/m$^3$, and 0.88-2.6 mg/m$^3$, respectively.[102] Sjogren, *et al.*[103] studied neuropsychiatric symptoms in 217 railroad track welders exposed to manganese with the aid of a questionnaire and found that welders exposed more than two years had a six-fold higher risk (OR = 6.25, 95% CI 1.95-20.0) of answering positively to three questions related to neurotoxicity including memory and concentration, affective changes, and symptoms of vegetative nervous system effects. In a follow-on study, Sjogren, *et al.*[104] examined 12 welders whose median exposure to welding fumes containing 22% manganese was 270 hours and showed decreased motor function in five tests and increased latency of event-related, auditory- evoked potential compared to a control group of welders who welded mostly iron. In a recent study, Luse, *et al.*[105] reported significantly-higher levels of manganese in blood (7.6x) and hair (3.2x) of welders versus unexposed controls and also observed that welders demonstrated memory deficits, and impairment of performance in motor function and attention assessment tests. Exposures in the work environment were measured between 0.003 and 2.6 mg/m$^3$. Another recent study by Sinczuk-Walczak, *et al.*[106] examined 62 welders and 13 battery production workers who have been exposed to manganese and found increased emotional irritability, memory impairment, concentration difficulties, sleepiness, and limb parathesias. The authors concluded that manganese exposures from <0.01 to 2.67 mg/m$^3$ (mean 0.4 mg/m$^3$) induce subclinical nervous system effects. A nerve conduction study of 57 flux-division workers exposed to manganese reported reduction in motor fiber conduction in 40% of the workers and reduced sensory fiber conduction in 56% of the subjects studied.[107]

A cross-sectional epidemiology study by Racette, *et al.*[108] was presented at a recent conference on Parkinson's Disease, and they reported on the screening of 2,081 welders and rated each welder according to accepted criteria for Parkinson's disease. They found that using liberal criteria for diagnosis of PD 11.2% of the patients had a diagnosis of definite PD and 13.5% of the patients had a probable diagnosis of PD. Using a more conservative criteria, these percentages were changed to 6.4% and 13.0%, respectively. The prevalence of parkinsonism in those identifying welding as their primary profession was 482/100,000 from which a relative risk (RR) of 3.8ss with a

95%CI of 1.7-8.4 can be calculated. Other calculations included those for welders' helpers (RR=3.7ss) and boilermakers (RR=6.4ss). In this abstract, the authors note that parkinsonism is more common in welders than in the general population.

Many other cases of welders developing parkinsonian symptoms have been reported in the open literature. One such report[8] involved a 44-year-old welder who had been involved with recycling railroad tracks made of steel alloy containing 11 to 14% manganese by welding with welding rods containing manganese for 15 years indoors without ventilation. An MRI of his brain provided visual evidence of cerebral manganese deposits. He developed irritability, headaches, insomnia, and lassitude; his symptoms progressed to poor memory, impaired cognition, and paranoid thoughts. Eight months after stopping work he experienced decreased hand grips, impaired vigilance and recall, impaired learning rate, amnestic processing, impaired perceptual and sequencing abilities, and dysarthric speech; at 10 months, he could not dress himself.[8] Another report described two long-term welders exposed to airborne manganese who experienced asthenia, dizziness, headaches, profuse sweating, disturbances in walking, spasticity in calves, and retropulsion.[109] A recent case report by Sadek, *et al.*[17] described a 33-year-old welder of manganese-steel alloys in confined spaces complaining of a two-year history of progressive cognitive slowing, rigidity, tremors, slowing of movements, gait instability leading to falls, cogwheel rigidity, tremor, and cock walk gait. An MRI of the brain confirmed ongoing manganese intoxication with an enhanced signal in the bilateral basal ganglia. Urine and blood manganese levels were elevated. Other recent individual cases of parkinsonism from welding fumes have been noted in Italy[110] and Japan.[111] Cases have been reported of a person involved with the coating of welding rods with manganese powder,[112] a manganese-exposed welder,[112] a case of manganese intoxication from cutting and burning of manganese steel, and from the use of manganese dioxide in ceramics.[113]

One of the biological markers for manganese intoxication from ongoing exposure to welding fumes and other sources is the appearance of a hyperintense T1 MRI signal in the globus pallidus section of the brain.[19] This marker was demonstrated in a welder who was using welding rods and sticks containing from 11-25% manganese resulting in manganese concentrations inside of the welding mask from 3 to 4.6 mg/m$^3$.[19] In this case, the signal returned to normal after cessation of exposure for six months.[19] Kim, *et al.*[97] found increased T-1 weighted MRI signal intensities in 73.5% of current asymptomatic welders versus 0% in unexposed controls. The authors concluded that this type of MRI response correlates well with blood manganese concentrations, but positive responses reflect only current exposure to manganese and not necessarily manganism.

## SYMPTOMS OF MANGANESE INTOXICATION - PARKINSONISM

There are several excellent reviews that discuss the consequences of manganese intoxication[2,5,10,114,115] including two World Health Organization (WHO) booklets.[3,116] Subjective symptoms of manganese intoxication include fatigue, headache, muscle cramps, lumbago, sialorrhea (increased saliva flow), loss of appetite, apathy, insomnia, somnolence, loss of memory, reduced concentration, diminished libido, impotence, slowing of movements, nervousness, irritability, aggressiveness, compulsive acts, emotional lability, and hallucinations.[24] Psychomotor signs include apathy, asthenia, compulsive acts, emotional instability, flight of ideas, hallucinations, lassitude and sleep disturbances,[113] while neurologic signs include clumsiness, diplopia, muscle cramps, muscle weakness, speech disturbances, and stiffness.[113] Other signs include depression, dysarthria (speech problems), expressionless facies, gait disturbances, muscular hypertonia, pathological laughter, propulsion/retropulsion, and tremors in the upper extremities.[113] Descriptions of this condition include monotonal speech with hypophonia, impaired writing and dexterity, sometime dystonic reactions, difficulty getting out of low chair, turning 'en bloc' and instability when walking backwards.[24] Some descriptions of the symptoms are similar to those described above,[10,17,18,25,114,117,118] while others mention fixed gaze and decreased mental status,[5] and a characteristic gait referred to as the 'cock walk'.[24] One report describes the third stage of manganism which includes bradykinesia, dysarthria, axial and extremity dystonia (impairment of voluntary movements), paresis, gait disturbances (slow and clumsy gait), cogwheel rigidity, intention tremor, impaired coordination and mask-like face.[5] The symptom "sequella" described for chronic manganese intoxication not only resembles Parkinson's Disease but is generally referred to as parkinsonism. Some believe that there exists a syndrome of neurological deficits referred to as "parkinsonism" or "idiopathic Parkinson's Disease" that differ only by genetic mutations expressed in individual cases[15] and age of onset.[1]

## PERSISTENCE AND IRREVERSIBILITY OF MANGANESE INTOXICATION

Parkinsonism from manganese exposure is thought to be progressive and irreversible[10,11,24,119] with the persistence of neurological effects more related to damage to the brain rather than the presence of high amounts of manganese;[120] thus, the neurotoxic effects and their progression persist long after exposure has ended.[117,121-124] This may be due, in part, to the lung deposits which result from inhalation of welding fumes and can release manganese into general circulation for long periods after exposure has ceased.[50] Huang describes six Taiwanese patients with chronic manganese induced parkinsonism whose symptoms worsened after cessation of exposure.[125] Onset of the disease is usually slow since it is thought to occur between 1-2 years of exposure.[4] A case report of a 44-year-old welder showed progressive parkinsonian symptoms at 8 and 10 months after stopping his exposure to manganese.[8] A meta-analysis of 18 published studies reported parkinsonism symptomatology 11 to 20 years post-exposure.[126]

## MANGANESE INTOXICATION AND PARKINSONIAN SYMPTOMS - HUMAN STUDIES

There are many reviews which describe human exposure to manganese and the central nervous system effects which are frequently referred to as parkinsonism or Parkinson's Disease.[2,3,5,10,114-116] I already have addressed several reports of parkinsonian symptoms related to manganese exposure in welding fumes; however, there are other sources of manganese exposure which have been reported to produce similar neurologic sequella including parkinsonism; some of which follow.

In a population-based, case-controlled epidemiology study, Gorell, *et al.*[127,128] reported a statistically significant (ss) odds ratio of 10.61ss for parkinsonian-like disease in those exposed for greater than 20 years to manganese. In a subsequent study published in 2004, Gorell, *et al.*[129] identified other risk factors for Parkinson's disease (PD) including greater than 20 years of exposure to excess manganese or copper, positive family history of PD, and smoking <=30pk-yrs or no smoking.[129] Santos-Burgoa, *et al.*[130] conducted a cross-sectional study of adult residents living in a manganese-contaminated environment, found increased blood manganese levels in the residents, and calculated statistically-significant (ss) relative risks of 11.7ss for deficiency in cognitive performance, 15.5ss for hand numbness, 6.7ss for motor strength, and 7.11ss for memory deficits. Another study of 273 people subjected to environmental contamination demonstrated a correlation between elevated blood manganese levels and deficits in coordinated upper limb movement and poorer learning and recall(ss).[131] An environmentally exposed group of 297 Canadians living near a closed ferroalloy plant demonstrated an association between increased blood manganese levels and decreased ability to perform regular rapid and precise pointing movements, decreased ability to attain maximum rotation speeds in alternating movements, and increased regularity of tremor oscillations.[132] In a study of environmental contamination in an area surrounding a ferroalloy plant, Lucchini, *et al.*[133] compared the prevalence of parkinsonism in the contaminated area with a non-contaminated control area and calculated a Standard Mortality Ratio (SMR) of 1.58ss(CI 1.41-1.76). As indicated previously, Racette, *et al.* recently reported on cross-sectional epidemiology study of 2,081 welders in which the calculated risk ratios ranged from 3.7ss to 6.4ss.[108]

Sixty-one ferroalloy workers exposed to manganese and 87 unexposed controls were studied using neuropsychological testing. Workers exposed to manganese containing dust had higher blood manganese levels than controls and showed higher prevalence of symptoms in alloy workers versus controls. Symptoms noted included irritability, loss of equilibrium and rigidity, tremors(ss), impaired memory and impaired motor function, and other neurobehavioral parameters.[134] Five cases of parkinsonism were reported in another ferromanganese alloy plant, and the authors stated that their findings ". . . justifies the presumption of a causal relationship between manganese and parkinsonism".[135]

Roels, *et al.*[28] first conducted a cross-sectional epidemiological study of 141 men exposed to inorganic manganese in an ore processing operation during a mean of 7.1 years versus the same number of unexposed controls and found significant alterations in simple visual reaction times, audioverbal performance, short-term memory capacity, and hand tremor. They concluded that exposure to manganese dust at concentrations of about 1 mg/m$^3$ for less than 20 years may result in clinical manifestation of manganese intoxication.[28] Another study by Roels, *et al.*[136] of 92 workers exposed to a mean level of 215 μg/m$^3$ respirable manganese dioxide in a battery factory compared to 101 controls reported that exposed workers performed neurofunctional tests (visual reaction time, eye-hand coordination, hand steadiness) in a less satisfactory manner than controls and that exposed workers demonstrated an increased risk of peripheral tremor. Roels, *et al.*[136] concluded that lifetime integrated exposure to 730 μgMn/m$^3$ × year of respirable Mn dust may increase the risk of peripheral tremor. Another study of 36 battery workers exposed to manganese reported that 22.2% demonstrated neuropsychiatric manifestations, 16.6% showed manganese psychosis, and one worker showed hemi-parkinsonism.[137]

Tanaka, *et al.*[27] studied manganese exposure in Pennsylvania industrial plants and found that 6% of the 117 exposed workers demonstrated signs of manganese intoxication. Increased signs of parkinsonism were reported in 30 men aged 20 to 64 who worked in a steel smelter when compared to 60 unexposed referents. The authors concluded that hygienic standards as low as 2.5 mg/m$^3$ were insufficient to protect workers from the central nervous system (CNS) manifestations of manganese.[29] A study comparing 30 manganese-exposed Swedish foundry workers with 60 unexposed controls reported deficits in simple reaction time, digit span, and finger tapping in the exposed versus the control group.[25] Exposures were from 1 to 35 years; concentrations were between 0.02 and 1.4 mg/m$^3$ manganese; and the mean age of symptomatic workers was 45.4 years.[25]

A study of Chilean miners exposed to manganese showed statistically-significant differences in occurrence of hand tremor, action tremors, and repetitive hand movement capabilities when compared with unexposed controls.[138] Another study of Chilean miners numbering 14 with exposures averaging 8 years reported psychomotor disturbances and neurologic symptoms,[26] while Mergler, *et al.*[139] reported significant differences in emotional state, motor functions, cognitive flexibility, and olfactory threshold between matched pairs of 115 workers employed in manganese ore production and unexposed controls. Other miners and those involved in manganese ore production have suffered parkinsonian signs and symptoms[21,23,26,117,118,120,135,138,140-144] as well as those employed in ferro-manganese alloy production,[22,24,119,125,145,146] those who have ingested manganese in drinking water,[5,147,148] those exposed to Maneb, a manganese-containing fungicide,[149,150] a single case of exposure to manganese via parenteral administration,[151] and inadvertent ingestion of potassium permanganate.[12]

Additional cases include that of a 52-year-old male involved in crushing manganese ore for about two years when he began to complain about difficulties in walking and diminished libido. Later he began experiencing euphoria, emotional incontinence, masked face, monotonous speech, "cock walk", increased muscle tone, weakness in upper and lower extremities, tremor of eyelids, and exaggeration knee jerks. Upon autopsy, he was reported to show degenerative changes to the basal ganglia section of the brain, particularly the pallidum.[120] This is consistent with early studies reporting basal ganglia damage from manganese with particular emphasis on the globus pallidus[72,82,84,91,93,152] Another account of two welders with 25 years in welding were exposed to airborne manganese up to 125 mg/m$^3$ and exhibited asthenia, dizziness, headaches, profuse sweating, as well as disturbances in walking, spasticity in the calves of one welder and dysmetry and repulsion in the other welder.[109] Emara[137] reported chronic psychosis, Parkinson's disease, and choreoathetosis (dyskinesia/tics) in 8 workers in a dry-cell battery plant using manganese dioxide; another report describes the development of parkinsonian symptom in a person using manganese powder to coat welding rods and a welder using manganese-containing welding rods.[112] Additional reports of welders suffering parkinsonian symptoms from manganese in welding fumes[110,111] and from other sources[14,71,72,74-82,84-94,152] are noted also.

## MANGANISM, PARKINSONISM AND PARKINSON'S DISEASE

Manganism and parkinsonism are considered synonymous. Parkinson's Disease is considered also to be part of the same continuum of neurological disorders controlled by an associated template of genetic mutations.[15] This being the case, it becomes difficult in some cases to differentiate between these conditions.[153,154] depending on age of onset and history of environmental exposures. Both genetic and environmental factors influence signs and symptoms[155] leading one to the conclusion that "Parkinson's disease is not one disease".[15] Referring to welding exposure to manganese, an industry document quotes, ". . . some permanent brain damage can result and symptoms are identical to Parkinson's Disease" (National Shipbuilding Research Program as referenced in "Materials Reviewed" Section of this report).

Symptoms of Parkinson's Disease have been elucidated by Calne, Gorell, and others to include resting tremor, rigidity, bradykinesia, impairment of postural reflexes and asymmetry of response,[127-129,153] while Olanow recently compared signs and symptoms of his "idiopathic PD" to manganese parkinsonism[156] citing resting tremor, asymmetry of response, good L-dopa response, normal MRI, decreased labeled fluoro-dopa striatal uptake, degeneration of neurons in the substantia nigra pars compacta, and elsewhere, and Lewy bodies as being characteristic of PD. He compares this with his concept of parkinsonism from chronic manganese intoxication citing signs and symptoms including early speech and balance dysfunction, symmetrical impairment, relative absence of tremor, distonia (grimace, cock walk), poor L-dopa response, high intensity T1 MRI signal in the globus pallidus, striatum and substantia nigra pars reticulata bilaterally, normal fluoro-dopa PET scan, degeneration of neurons in the globus pallidus, and absence of Lewy bodies.[156] Olanow[156] also states, "The clinical syndrome,

response to levodopa, imaging studies with MRI and PET, the pathological features all help to distinguish these two conditions (ed. note: parkinsonism from manganese vs PD) and permit correct diagnosis to be established". Pal and Calne[11] cite behavioral changes, loss of appetite, apathy, somnolence, loss of memory, reduced concentration, loss of libido, parkinsonian features (difficulty getting out of low chair, anteropulsion, retropulsion, turning "en bloc" , problems walking backward), dystonia with severe gait disturbances, and "cock walk" as being characteristic of manganese-induced parkinsonism. Kim, *et al.*[154] describes Mn parkinsonism with lack of tremor as predominant feature, early dystonia, early postural impairment, peculiar walking, cock walk, difficulty in backward walking, and failure to respond to levodopa therapy as compared to PD.

On the other hand, Racette, *et al.*[1] recently reported on a study of 15 career welders exposed to manganese which he compared to two control groups composed of cases of diagnosed idiopathic PD. They could find no difference in frequency of tremor, bradykinesia, rigidity, asymmetric onset, postural instability, family history, clinical depression, dementia or drug induced psychosis. He concluded that the only difference between the welders and the patients with idiopathic PD was the age of onset of the disease.[1] Others also disagree with the differences espoused above. A case report involving a 48-year-old welder with PD symptoms exhibited a masked face, right side (arm and leg) resting tremor, and bradykinesia.[154,157] A 56-year-old foundry worker exposed to manganese reportedly showed resting tremor on the left side, bradykinesia, no dystonia, postural instability, cock walk, and difficulty walking backwards[154] and another case of a 44-year- old welder demonstrating a progressive tremor, with later rigidity and akinesia.[158] Thus, it would appear that the pattern of symptomatology is as diverse as the patients themselves with some commonality in a general sense. While Olanow[156] suggests asymmetry and resting tremors in cases of PD versus symmetrical impairment and absence of tremor in manganese-induced parkinsonism, a study of Chilean miners with heavy exposures to manganese describes resting and action tremors in their exposed patients.[138] In addition, battery workers exposed to manganese dust are reported to show increased risk of peripheral tremor[136] and hemi-parkinsonism.[137] Other reports of those exposed to manganese have described tremors.[4,10,12,17,22,24,28,113,120,132,134,138]

MRI imaging of specific regions of the brain also has been cited in an attempt to differentiate manganese-induced parkinsonism from idiopathic PD.[11,156] Indeed, there are reports of hyperintense T1 MRI signals in the basal ganglia region signaling ongoing exposures to manganese.[8,17,19,97] This is confirmed with observed enhanced signals from the striatum, globus pallidus, and substantia nigra pars reticulata regions of brains in manganese-exposed non-human primates;[159,160] however, there are also reports of this signal intensity returning to normal after the exposure period has ended.[8,19,151,157] Recent reports by Calne, *et al.*[161,162] describe no increased intensity of response to the MRI probe in four patients with chronic manganese intoxication due to occupational exposures despite clinical progression of parkinsonism.
Another brain imaging technique, albeit somewhat experimental, positron emission

tomography (PET), using radioactive fluorodopa has been applied to this problem and has been put forth as definitive proof of distinct pathological differences between manganese parkinsonism and PD.[11,112,156] There are indeed reports of decreased uptake of fluorodopa in cases described as idiopathic PD.[112] One such case describes reduced striatal uptake particularly in the posterior putamen with loss in dopaminergic cells in the substantia nigra pars compacta.[163] Also, in primates intoxicated with manganese, the fluordopa PET scan was reported to be normal;[161,162] however, in the midst of this apparent consistent response is a report of four Taiwanese patients suffering manganese-induced parkinsonism who showed mildly reduced fluorodopa binding in the caudate and low normal range of binding in the putamen.[164] Other contradictory reports[1,161] include reduced fluorodopa uptake in the left putamen of a 48-year-old welder,[157] and two out of 15 welders with symptoms typical of idiopathic PD demonstrated reduced fluorodopa uptake particularly in the posterior putamen.[1] Another supposed marker for differentiating manganese-induced parkinsonism and PD relates to the therapeutic value of L-dopa. This relates to the PET discussion above, since the latter relies on a destruction of dopamine receptors to produce a PET scan showing reduced uptake of fluorodopa. Now we are considering a response to that depletion by supplementing with levodopa therapy. Again, as with the PET technique, there are inconsistencies. The presumption is that those with PD will respond well to levodopa therapy, and those with manganese-induced parkinsonism will not respond.[21,143,154,156,165,166] There are reports showing that PD patients do not respond to levodopa therapy,[167] and there are reports of welders and others who have been exposed to manganese responding well to levodopa therapy.[1,24,125,126,142,140,154] A study of Chilean manganese miners reportedly showed dramatic improvement in response to levodopa therapy,[142] while another study of 15 welders exposed chronically to manganese also demonstrated improvement in their symptoms after levodopa therapy.[1] One report concludes, "It remains unanswered whether Mn causes the degeneration of presynaptic dopaminergic nerve terminals and even PD",[154] while another report concludes, "There are conflicting reports about the efficacy of these treatments . . .".[11]

The presence of Lewy bodies as a marker for PD is also in question. Lewy bodies have been found in autopsy material from some PD patients but not from others.[167] Patients with long-term PD symptomatology have not shown Lewy bodies in the substantia nigra area of the brain,[168,169] while others with no neurologic signs during their lifetime have Lewy bodies in substantia nigra brain tissue.[170-172] One report describes a 44-year-old female exposed to manganese and demonstrating parkinsonism with Lewy bodies.[158] One study by Calne and Mizuno concludes, "Lewy bodies in the substantia nigra are not an acceptable hallmark of Parkinson's Disease".[15]

Concerning pigment loss in the substantia nigra, another suggested marker for PD, there are reports of PD patients with and without pigment loss.[167] The substantia nigra pars compacta is thought to be another target area for PD with prominent depigmentation, neuronal loss, and Lewy bodies in the substantia nigra pars compacta, the locus caeruleus, and the dorsal nucleus of vagus.[120,154,173] On the other hand, manganese-related parkinsonism is thought to involve degeneration of the globus

pallidus with some damage to the putamen, caudate nucleus, and the substantia nigra pars reticularis.[120,154] Less frequently observed is a decrease in myelinated fibers with astrocyte proliferation[120,154] and neuronal loss in the substantia nigra with gliosis.[167] Also observed in cases of manganese intoxication is marked degeneration in the substantia nigra pars compacta.[158,174]

In addressing these apparent inconsistencies in defining idiopathic PD as being something different from parkinsonism induced by manganese, Calne and Mizuno[15] add reason to the discussion by pointing out that there are at least 12 different gene locations where mutations have been linked to Parkinsonism. This observation demands a variety of disease patterns and brings the authors to the conclusion that Parkinson's Disease is not a single disease but a syndrome with many causes. Acknowledging the strong influence of environmental factors on an overlay of genetic variability, he suggests classification of the syndrome as being "primarily environmental" or "primarily genetic". This is a scientifically acceptable concept to explain the variability of signs and symptoms involved in this syndrome, and it further offers support for Racette, *et al.*[1] who determined that early age at disease presentation was the only factor that separated his 15 welders from two control groups with idiopathic PD. They concluded "Parkinsonism in welders is distinguished clinically only by age at onset, suggesting welding may be a risk factor for PD. These preliminary data cannot exclude a genetic contribution to susceptibility in these exposed individuals".[1]

Thus, it would appear that the distinction between manganese-induced parkinsonism and Parkinson's Disease is not obvious. In order to get a better understanding about current scientific thinking in this matter, consider the following quotations from recent publications: "All of the findings showed that the welder has idiopathic parkinsonism with superimposed manganese exposure" (Kim *et al.*, 1999);[157] "The third and most provocative interpretation is that our patients have PD specifically induced by Mn exposure"(Kim *et al.*, 2002);[154] ". . . these results indicate that PD is usually caused by an accumulation of transient environmental events" and "Of course there is interaction between the environment and the genome; in some disorders inheritance establishes the susceptibility and environment triggers the pathology"; (Fuente-Fernandez and Calne, 2002);[175] "So genetic heterogeneity is so marked and so many Parkinsonian loci have been identified, that it becomes impossible to defend the notion that Parkinson's Disease is one disease. The idea of there being only one Parkinson's Disease is rendered even more untenable when we take into account evidence that most cases of Parkinson's Disease are caused by environmental rather than genetic risk factors" and, in conclusion, "Parkinson's Disease is not one disease"(Calne and Mizuno, 2004);[15]

While it is clear from the above discussions that there is a definite causal connection between exposure to manganese and parkinsonism, in order that there will be no doubt that there is a causal relationship, I have conducted a causation analysis using the criteria of Sir Bradford Hill.[16] Causation analyses using these criteria have become an accepted approach to causation by the International Agency for Research on Cancer, the Surgeon General of the United States, and others.

## CAUSATION - THE HILL CRITERIA

A. B. Hill[16] has described criteria for establishing general causation. These criteria have been refined somewhat since his original paper but have not changed significantly. The Hill criteria are widely accepted, and the International Agency for Research on Cancer uses many of these criteria as part of their classification scheme for carcinogens. The Hill criteria apply to human studies and propose a set of requirements to be met in order to establish causation. Some of the criteria allow for the use of data from controlled animal studies in order to establish the target organs and mechanisms of action of particular toxicants. We will apply this criteria to the possible establishment of a causal connection between exposure to manganese contained in welding fumes and the parkinsonian condition described above.

### 1. Strength of Association

*The essence of this criteria involves an assessment of the extent to which a particular disease coincides with a particular exposure. The incidence of the disease does not have to be high in order to establish a strong association. In the case of a rare disease, the finding of even a few cases within a small population who have been treated with a particular drug or exposed to a particular chemical entity would be of great significance.*

In this report I have described clearly the welding environment and exposure to airborne manganese within that environment, including airborne manganese generated from welding rods of various types.[5,17,19,45,59-68,95-97,101,102,104,106,109,112,176] I have provided strong documentation of the parkinsonian symptomatology reported in welders using manganese electrodes[1,8,17,97,103-107,109-112] I also have described other environments in which manganese exposure has resulted in symptomatology that has been described as parkinsonism.[5,12,14,21-29,71,72,74,76-82,84-87,89,90,92-94,108,113,117-120,125,130-151,177-179]

Having described the vast basis of literature supporting a causal relationship between manganese and parkinsonism, the review publications cited above provide overviews and supportive commentary on the strength of this association.[2,3,5,10,14,18,75,77,81,83,88,91,114-116] One epidemiology study in particular describes an odds ratio (OR) of 10.61ss (95% CI 1.06-105.83) for a causal relationship between a greater than 20 years' exposure to manganese and Parkinson's disease.[127-129] It should be noted that some believe that the only differences between idiopathic Parkinson's Disease and parkinsonism from manganese (manganism) is the age at which the disease presents.[1,26,125,180] Others have pointed to the numerous genetic mutations relating to parkinsonism and attribute early presentation of symptomatology to the influence of "environmental" factors such as manganese exposure.[15]

An epidemiological study published recently demonstrated a causal association between habitation in a manganese-contaminated environment resulting in elevated blood manganese levels and statistically-significant increased relative risk (RR) of deficient cognitive performance (RR = 11.7ss), of hand numbness (RR = 15.5ss), of decreased

motor strength (RR=6.7ss) and of memory deficits (RR=7.11ss).[130] A very recent presentation of a cross-sectional epidemiology study by Racette, *et al.*[108] reported risk ratios from 3.7ss to 6.4ss for those having primary occupational exposure to manganese as welders, welder's helpers, or boilermakers. Independent of any occupational exposure, 273 residents were exposed environmentally resulting in blood manganese levels ranging from 2.5 to 15.9 μg/L and dose-related decrements in coordinated upper limb tasks, and learning and recall, suggesting a continuum of CNS dysfunction related to manganese exposure.[131] Another study of environmental exposure to manganese was described in 297 residents of Quebec living near a closed ferroalloy plant. At blood manganese concentrations of greater than 7.5 μg/L, impairment of ability to perform regular, rapid, and precise pointing movements, decreased ability to attain maximum rotation speeds in rapid alternating movements, and increased regularity of tremor oscillations were noted.[132] Parkinsonism related to manganese exposure in the ferroalloy[5,22,24,119,125,145,146] and mining industries[21,23,26,117,118,120,135,138-144] have been noted already in this report. It should be clear that the parkinsonian symptomatology resulting from manganese exposure can result from exposure to manganese from a number of different sources and that the strength of the causal link between manganese exposure and parkinsonism is very strong and well supported in the peer-reviewed literature.

**2. Consistency of Association**

*Hill*[16] *asks the question, "Has it been repeatedly observed by different persons, in different circumstance and times?". In other words, have similar findings been observed by different observers.*

I have described peer-reviewed studies demonstrating a cause and effect relationship between manganese exposure and parkinsonism-like symptoms in welders,[1,102-104,106-108,141] including individual case reports of those exposed to welding fumes,[1,8,14,17,71,72,74,76-82,84-87,89,90,92-94,109-111] in case-control studies,[1,127-129] in those involved in the ferroalloy industry,[5,22,24,119,125,134,135,145] in those exposed to manganese in the environment,[127,130-133,144,178] in those involved in mining or processing manganese ore,[21,23,25-29,120,135,138-143] in those exposed by parenteral nutrition,[151,181,182] in those exposed to a manganese-containing fungicide,[149,150] in those exposed to manganese dioxide in battery factories and coating of welding rods,[112,136,137] in those exposed to manganese in drinking water,[5,147,148] and in those involved with other activities involving manganese exposure.[12,113,146] In addition, there is no geographical limit to the causal connection between manganese exposure and parkinsonism since the link has been reported in Chile,[26,138] India,[118] the U.S., China and Taiwan,[24,125] South Korea,[97] Morocco,[117] Israel,[149] Sweden,[25] Egypt,[90,93,144] Cuba, Japan,[111,151] the former Soviet Union. Clearly, I have demonstrated that manganese exposure under a variety of exposure scenarios, including inhalation of welding fumes, is capable of producing neurotoxicological effects characterized as parkinsonism-like symptomatology. I have demonstrated that these effects know no geographical boundaries; thus, the causal link between manganese and parkinsonism knows no geographical boundaries or limitations in terms of exposure scenario. The causal link has been consistently observed.

### 3. Specificity of Association

*The specificity of an association describes the precision with which the occurrence of one variable will predict the occurrence of another. This criterion overlaps the strength of association to some extent but focuses more on the direct link between a specific disease and a specific cause for that disease. When dealing with human populations, this specificity is rare.*

Exposure to manganese, whether it be by ingestion of contaminated drinking water or by inhalation of dusts or fumes containing manganese, produces neurological effects which are thought by some to be identical to Parkinson's Disease in man. While the symptomatology is similar to that of Parkinson's Disease (PD), some believe that there are some distinct differences.[11,24,112,120,125,183-186] In order to firmly establish a causal connection between manganese intoxication and parkinsonism, it is important to understand the issues defining idiopathic PD and manganese-induced parkinsonism. Although I have addressed this issue in detail previously in this report under the heading "Manganism, Parkinsonism, and Parkinson's Disease", the following is a re-iteration of some of that discussion.

In a recent study, Racette, *et al.*[1] reported a comparison of 15 career welders with two groups of controls both having been diagnosed with idiopathic PD. One group of controls with idiopathic PD was sex and age-matched. The authors found no differences in frequency of tremor, bradykinesia, rigidity, asymmetric onset, postural instability, family history, clinical depression, dementia or drug-induced psychosis between the welders and the two control groups. PET scans on two of the welders showed depletion of l-dopa receptors in the posterior putamen as is typical in idiopathic PD. Although these investigators could not rule out genetic susceptibility as a contributing etiologic factor, they concluded that the one distinguishing difference between the welders and those with idiopathic PD was the age of onset of the symptomatology.[1]

Calne and Mizuno[15] in a publication entitled, "The Neuromythylogy of Parkinson's Disease" have recently described several genetic mutations that have been related to parkinsonism and, even in the face of published information to the contrary, have suggested that parkinsonism and Parkinson's Disease represent a continuum of disease rather than separate entities. They describe disease states as being "primarily genetic" or "primarily environmental", depending on the interaction of genetic and environmental factors involved in the individual case.[15] This conclusion is reasonable since attempts to distinguish between idiopathic PD and manganese-induced parkinsonism have only been successful in a limited number of cases.[1]

PD is a classical basal ganglia disease but does not involve any accumulation of manganese in brain tissue.[183] While manganese specifically affects the striatum, global pallidus, and substantia nigra reticulum, idiopathic PD is thought to affect the dopaminergic neurons of the substantia nigra compacta, resulting in prominent

depigmentation and neuronal loss.[112,120,184,185] As a result of this apparent difference related to the dopaminergic receptors, cases of idiopathic PD reportedly respond well to L-dopa treatment while cases of manganese may respond only briefly or not at all to the same treatment.[11,165,184] Of course, there are exceptions to this difference.[1,125,126] Positron Emission Tomography (PET) scans using $^{18}$F-dopa and other markers show reduced uptake of the tracer in the left putamen in cases of idiopathic PD, but show normal responses in some cases of manganese intoxication. This reflects the destruction of 40-60% of the dopaminergic receptor sites in the case of idiopathic PD.[11] One study of only two manganese-exposed welders reported opposite responses to PET scans,[112] and another study described above has reported positive findings in at least two welders.[1] Normal PET scans have been reported in studies of Rhesus monkeys exposed to manganese.[164] which is consistent with preservation of nigrostriatal dopaminergic pathway despite parkinsonian type deficits. This finding is also consistent with an apparent lack of, or transient response to, L-dopa in manganese parkinsonism[164] in some cases but not in others.[1]

On the other hand, Magnetic Resonance Imaging (MRI) brain scans of workers currently exposed to manganese are reported in some cases to show manganese accumulation,[97,151,181,182,187] whereas those with idiopathic PD show no manganese accumulation in brain tissue.[8,186] Similar MRI findings of manganese accumulation have been reported in monkeys[159,160,164,183] Again, documented cases of neurotoxicity in manganism patients have demonstrated negative findings in MRI scans.[112,161]

Age of presentation of symptoms of parkinsonism would appear to be the major distinguishing factor between parkinsonism from manganese exposure and idiopathic PD.[1] The predictability of manganese neurotoxicity is very high, and the manifestation of the resulting disease appears much earlier in life than one would predict for idiopathic Parkinson's disease. One study relating to this phenomenon reports a mean age of onset of parkinsonism-like symptomatology of 46 years, while that for idiopathic PD is 63 years with the difference being statistically significant at the 99.99% level.[1] Another study[125] reported the ages of six patients who developed parkinsonism after manganese exposure. The ages were 50, 41, 53, 41, 44, and forty-four years resulting in a mean of 45.5 years. In a study of Indian manganese mining,[180] the youngest age of appearance of parkinsonism was 17, while the oldest was 44 years, this being consistent with the author's prior study.[1] In Chilean miners, the age range for development of parkinsonism was 21 to 50 years.[26] Age is a major distinguishing factor in establishing a causal connection between manganese exposure and parkinsonism-like symptomatology; and presentation of symptomatology at an early age may very well reflect the "primarily environmental" contribution to the appearance of the disease.[15]

Toxicological effects of manganese consistent with those observed in man have been consistently described in monkeys,[52,54,124,136,160,183,188,189] rats,[56,57,190] guinea pigs,[55] and mice.[191-193]

As discussed above, the toxicological response to manganese intoxication, whether it be from welding fumes, from contaminated water, from ore processing, or from battery fabrication, is identical not only in man but in animals. Thus, the consistency of the causal link has been established. The major distinguishing factor between parkinsonism from manganese exposure and idiopathic PD is the age of presentation of symptoms.

**4. Temporality**

*Hill[16] asks "Which is the cart and which is the horse?" If a disease state exists prior to exposure to a medication, the exposure may exacerbate the disease but may not have caused the disease. The appearance of a diseased state must follow treatment with the medication being addressed.*

Exposure before disease presentation is a simple concept, but on many occasions the timing of the appearance of disease symptomatology does not coincide with what is known about the disease. For example, assume that a person was exposed by inhalation to hexavalent chromium and developed lung cancer two years later. In this case, a causal link cannot be established because of a combined violation of temporality and coherence. The published science tells us that the latency period (time from first exposure to appearance of disease) for developing lung cancer from hexavalent chromium is about 20 years. Thus, both the temporality and coherence factors are violated in the example since the disease appears only two years following the initial exposure to hexavalent chromium. This observed cancer is both inconsistent with what is known about lung cancer development from exposure to hexavalent chromium and the timing of the occurrence of the cancer.

The temporality issue related to manganese is much different and less definitive than the example cited above. Manganese can be an acute toxin with neurological manifestations resulting from a single exposure or a chronic toxin with neurotoxicity expressed after many years of exposure.[10,18] Some examples of acute toxicity can be found in a monkey study in which a single injection produced manganese accumulation in the brain and tremors within three weeks,[53] and a human study of ingestion of potassium permanganate resulting in neurological symptoms within two weeks.[112]

Other studies[188] in monkeys report neurological symptoms similar to those found in man 9 to 24 months after injection of manganese;[124] accumulation of manganese in brain tissue after a 10-month inhalation study in Rhesus monkeys;[52] a 2-year inhalation study showing accumulation of manganese in brain tissue;[54] and a 5-month inhalation study where parkinsonian symptoms presented at 5 months with manganese accumulation and brain damage.[190]

Other than the case of intoxication indicated above,[112] most human exposure cases resulting in parkinsonian symptomatology involve more lengthy exposures. Some examples include: greater than 20 years of exposure to environmental manganese;[127-129] manganese ore miners with 5+ years of exposure and 5 years of latency,[138] 1-16 years of exposure,[26] 4-16 years of exposure,[118] 0.5 to 17 years of exposure[180] and 0.5 to 25 years of exposure;[144] 15 years of exposure in a ferroalloy plant;[134] 3 to 13 years in a Taiwanese ferromanganese smelter with induction time from 1 to 12 months;[125] 1 year latency in a dry cell battery plant;[137] 1 to 35 years of exposure in a Swedish foundry;[25] 15 years of welding indoors with 8 to 10 months latency after last exposure;[8] 25 years of welding.[109] Thus, in the case of neurological effects from exposure to manganese, the exposures precede the development of symptoms and are usually chronic in nature. Exposure and timing of symptom development are clearly consistent with this criterion of temporality when considering manganese intoxication.

**5. Biological Gradient**

*Dose-response is the foundation of good toxicological studies. The higher the dose or the longer the treatment, the more severe the response or the more prevalent the response. Dose cannot only be expressed as a single dose producing an acute response, but also by specifying the daily dose and treatment period. The latter is more appropriate in this situation.*

Although a level at which no toxicological effects have been found has been difficult to find in monkeys,[188] increasing behavioral deficits have been correlated with manganese content in the globus pallidus and substantia nigra portions of the brain in a dose-dependent manner.[183] In a study in man involving 297 residents living near a ferroalloy plant, blood levels of manganese during ongoing exposures were found to be correlated with frequency dispersion and harmonic indices as indications of neuromotor deficits.[132] A study of neuropsychological parameters measured for 61 male ferroalloy workers and 87 controls showed not only a positive correlation between ongoing exposure and blood-manganese levels but a dose-dependent correlation between cumulative exposure index and some neurobehavioral deficits.[134] A cross-sectional study sample of residents living in a manganese-contaminated environment demonstrated a dose-related deficiency in cognitive performance related to cumulative exposure to manganese.[130]

A study of low-level environmental exposure of 273 people with blood-manganese concentrations ranging from 2.5 to 15.9 μg/L reported a dose-response relationship between blood manganese concentration, an indication of current exposure, and changes in upper limb movement, poorer learning and recall. Both responses were statistically significant.[131] These findings are consistent with another environmental exposure study which concluded that parkinsonism incidents increase with increasing exposure to manganese and age.[178] Measurements of T1-weighted MRI signals have been shown to be a good indicator of ongoing manganese exposure in workers exposed to manganese.[97] Dose-related increases in incidence of tremors, rigidity, gait

disturbances, and other parkinsonian effects in those aged 50 and over were found with increasing concentrations of manganese in drinking water.[148]

There are yet other studies which demonstrate dose-related neurological and neurobehavioral effects simulating parkinsonism in animals and in man as a result of exposure to manganese.[2,3,5,10,18,114,116] I have adequately demonstrated that the neurological and neurobehavioral effects referred to as parkinsonism are related in a dose-dependent manner in both animals and man and have thus fulfilled the requirements of this criterion.

### 6. Plausibility and Coherence

*I will consider these criteria together since they impinge on the same theme voiced by Hill[16] with regard to coherence ". . . the cause and effect interpretation of our data should not seriously conflict with generally known facts of the natural history or biology of the disease". In addition, hypotheses based on sound scientific principles should be presented to explain the phenomena under consideration and to demonstrate the plausibility of the causal conclusions being reached. It is desirable to provide experimental evidence to support the hypothesis, but this is not always available.*

We have demonstrated that manganese can be absorbed through the lungs or GI tract,[2,50,105] and it is well known that upon inhalation manganese dust or fumes can be absorbed into the circulating blood[50,105,190] and is deposited in brain tissue,[50,55,57,58,191,194] accumulating in the caudate nucleus, pallidum, and putamen[52,54] in both man and animal. The pathway to the brain is thought to occur via a carrier- mediated uptake and transport through the blood-brain barrier.[195,196] Further, it is well known that manganese accumulates in brain tissue during continuing exposure situations[5,11,52,97,151,160,164,181-183,186-188] resulting in brain damage mostly in the globus pallidus, putamen, and caudate nucleus.[53,72,82,84,91,93,152,160,189] This brain damage presents as neurological and neurobehavioral signs as described above and is reminiscent of, if not identical to, Parkinson's Disease[53,80,82,84-87,160,189] which is a classic basal ganglia disease.[183] The basal ganglia are associated with the regulation of movement and organization and expression of behavior sequences[183,197] which is consistent with parkinsonian symptomatology. "Manganese intoxication is a well-known cause of parkinsonism and dementia."[12]

Upon inhalation of welding fumes or of other respirable dusts, manganese is eliminated about four times slower from the brain than when it is administered subcutaneously in monkeys.[50,188] This is a result of a slow lung release of manganese into general blood circulation.[50] The persistence of neurological effects resulting from manganese inhalation[17,122-125] may be much greater than that resulting from ingestion of manganese in drinking water because of slow release from the lungs after inhalation of manganese-containing dust or fumes.[50,188,198]

Various studies have shown that manganese is normally cleared rapidly from the brain,[8,50,188] being excreted mainly in feces.[8] Even though manganese may be cleared from the brain, the residual effects of the resulting pathology are both progressive and irreversible.[5,8,10,11,24,50,117,119-126,138,144,198]

It is clear from the above discussion that manganese reaches and damages the brain when inhaled, ingested, or injected. Manganese damages the basal ganglia. Although injury to the brain is diffuse, there are reports that it primarily effects the cells of the striatum and globus pallidus.[5] Several mechanisms involving dopamine, serotonin, gamma-aminobutyric acid, and their receptors have been proposed.[11] Reactive entities and processes that may be involved in producing this brain damage from manganese include autooxidation of dopamine, cytotoxic free radicals, depletion of thiols by superoxide radical formation, mitochondrial toxicity, and others;[114] but the true mechanism is still not well understood.[11,196,199,200]

It has been reported that one of the major observations that distinguishes manganese parkinsonism from idiopathic Parkinson's Disease (PD) is the age of presentation of the disease.[1,26,102,125,180] In many cases,[125,126] manganese parkinsonism (MP) does not respond as well to levo dopa therapy as does PD,[11,17,125,156,184] mainly because manganese is thought to damage the post-synaptic structures of the basal ganglia.[184] There are definite exceptions to this concept as indicated above. PD is thought to be caused by a reduction in the level of dopamine in the caudate nucleus due to the death of dopaminergic cells of the subtantia nigra[112] and neuromelanin, an intracellular polymer of dopamine-derived quinones is greatly reduced.[184] Thus, the primary focus of neurodegeneration in idiopathic PD is thought to involve the integrity of the nigrostriatal pathway with reduced labeled L-dopa uptake signaling injury.[112] There are exceptions to this in that some patients suffering chronic manganese intoxication do respond to L-dopa.[1,125,126] Positron Emission Tomography (PET) scans using $^{18}$F-labeled dopamine show some normal responses in cases of manganese parkinsonism (MP),[186] but reduced uptake in the left putamen in cases of idiopathic PD.[112,186] This is consistent with 40-60% loss of dopaminergic receptor cells in the nigrostriatal pathway in PD but not MP[112,164] and is consistent with PD affecting the dopaminergic neurons of the substantia nigra compacta[185] which is pigmented; whereas, the effects of MP are diffuse.[24,125] Again, there are exceptions to this PET finding in patients with manganism.[1,161] Another distinguishing difference between PD and MP is the fact that MRI brain scans show manganese accumulation during ongoing exposures to manganese in MP but not in PD.[186]

Histopathological differences are thought also to exist between cases of MP compared to PD. Cases involving manganese exposures have shown decreased myelinated fibers with astrocyte proliferation in autopsy material of a manganese miner.[120] Another case of manganese intoxication reported degeneration of the globus pallidus especially in the medial segment followed by less severe degeneration of the putamen, caudate nucleus, and the substantia nigra reticulum.[11] In contrast, autopsy materials examined from cases of idiopathic PD show prominent depigmentation and neuronal loss in the

substantia nigra, locus cearuleus, and dorsal nucleus of the vagus.[120] Lewy bodies and neurofibrillary tangles in the cerebral cortex were also found in the PD patient. Lewy bodies are thought to be a marker for PD in substantia nigra,[120,156] but some patients diagnosed with PD have been reported without Lewy bodies in the substantia nigra.[168] This, as well as other perceived differences between parkinsonism from manganese exposure and idiopathic PD, have been questioned, and the variability attributed to the multiple genetic mutations already associated with idiopathic PD rather than a true distinction between the two disease states.[15] An extensive discussion of these differences and justification for the conclusion "Parkinson's Disease is not one disease"[15] is found in the section of this report entitled, Manganese, Parkinsonism, and Parkinson's Disease.

I have presented a coherent scenario for injury as a result of inhalation of manganese from welding fumes and other sources. I have described inhalation of manganese dust and deposition in the lungs, and the slow release and translocation of manganese from the lung to specific areas of the brain producing pathology which results in neurological and neurobehavioral symptomatology frequently referred to as parkinsonism. Making use of sound scientific principles, I have presented plausible mechanisms for this action and have provided experimental data from animal studies to support the concepts and mechanisms presented to explain the toxicity profile of manganese. I have further provided ample evidence for questioning the differences between manganese-induced parkinsonism and idiopathic Parkinson's Disease leading to the conclusion that there are differences representing a continuum of disease states based on environmental influences on genetic susceptibility, rather than that there are two separate and distinct disease entities. As a result of the information presented, the requirements for plausibility and coherence have been fulfilled.

## 7. Experiment

*Although human clinical trials are relied upon to establish the efficacy of drugs, and epidemiolgy studies are used in establishing causation relating to adverse drug reactions , animal experimentation is extremely useful in demonstrating concepts used to explain some of the human findings. In addition, studies of the effects of chemicals on cellular processes have also proven useful in being able to understand the mechanisms involved in the toxicological processes being studied.*

I have presented various studies in humans exposed to manganese in the environment[127,128,130,132,133,178,194] and in occupational settings such as welding,[102-106] mining,[138] ferroalloy production,[25,27,28,134,135,139] and in dry-cell battery production,[136,137] among others. These studies, for the most part, are far less controlled than studies which have been carried out in animal models. While there are numerous toxicity studies describing the effects of manganese on animal models,[3,10,18,56,116,152,201-207] I will limit my discussion to some of those pertinent to the establishment of a causal connection between manganese exposure and neurological/neurobehavioral effects.

Human studies describe parkinsonism in response to manganese exposure, and animal studies, mostly in monkeys, also show similar symptomatology. For example, monkeys exposed subcutaneously to manganese for five months exhibited unsteady gait with subsequent action tremor, progressing to loss of power in both limbs with movements of hands and feet being described as clumsy.[189] Another monkey study described hand tremors with hyperkinetic behavior and hyperexcitability,[53] while others reported unsteady gait and hypoactivity when animals were exposed to manganese by subcutaneous injection.[160] Mice also have shown behavioral alterations in response to manganese intoxication.[52] A study which involved intravenous injection of manganese in monkeys describes the signs and symptoms as being suggestive of involvement of the basal ganglia, especially the globus pallidus and substantia nigra.[183]

Magnetic Resonance Imaging (MRI) has demonstrated significantly increased manganese concentrations in the brains of monkeys treated intravenously with manganese, especially in the globus pallidus and substantia nigra regions of the brain.[159,160,164,183] Several other monkey studies have demonstrated manganese accumulation in the basal ganglia,[52-54,160,189] including a 2-year inhalation study which concludes, "Within the basal ganglia, the globus pallidus would appear to be the most vulnerable area affected by manganese".[54] Manganese deposition in brain tissue also has been demonstrated in mice[190] and in guinea pigs.[55] Rhesus monkeys exposed intramuscularly to manganese for 9 to 24 months are reported to show brain pathological changes similar to those noted in humans.[124]

An inhalation study in mice showed accumulation of manganese in brain tissue.[191] Still other studies demonstrated the translocation of inhaled manganese from lung to brain in rats[190] and guinea pigs.[55] Mice also have demonstrated manganese toxicity.[191-193,208] Animals also have been utilized in the study of manganese metabolism[8,50,188,209] and mechanism of action.[2,5,10,11,56,57,139,164,195,196]

The experimental data presented in this report clearly supports a causal relationship between manganese exposure and translocation of manganese to the brain from various exposure routes, as well as brain pathological changes in the basal ganglia of the brain. The animal studies are consistent with those in man, and the neurological and neurobehavioral manifestations are also consistent.

**8. Analogy**

*Are there other drugs, chemicals or conditions that simulate the causal relationship which is under scrutiny? Are there other similar situations that parallel the events relating to the causal connection addressed herein?*

It is difficult to identify an analogous agent that causes the identical neuropathology as does manganese. There are certainly other agents that cause parkinsonism. Risk factors for PD include > 20 years' exposure to copper, lead and copper, copper and iron, or lead and iron,[127-129] a positive family history of PD in first or second generation relatives,

occupational exposure to farming, occupational exposure to insecticides and herbicides, and smoking <=30pk-years or not smoking.[127-129] Drugs such as dopamine receptor blockers, dopamine depleters and lithium are also risk factors for PD as are diseases such as Wilson's disease, Huntington disease, neuroacanthocytosis, Hallervorden-Spatz disease, anoxic encephalopathy and chemical agents such as manganese, mercury, methanol, and carbon disulfide.[17] Idiopathic Parkinson's disease would at the outset appear to be a very close analogy; but, as pointed out in a 2004 publication by Olanow[156] and by the discussions found above, parkinsonism from manganese exposure differs from true idiopathic PD only by age of presentation,[1] if at all. Those exposed to MPTP exhibit a disease which mimics the anatomic and clinical features of Parkinson's Disease,[153, 210] and MPTP is considered by some to be a cause of PD. This could be considered as an analogous situation, but a true analogy for the causal connection between manganese and parkinsonism is tenuous, at best. In discussing his criteria, Hill[16] makes it clear that all of the criteria need not be met in order to establish causation.

## CONCLUSIONS AND OPINIONS

There should be little doubt at this point that excessive inhalation exposure to manganese from inhalation of welding fumes can cause a parkinsonism that is similar, if not identical, to Parkinson's disease (PD) but presents at an earlier age as a result of environmental influence on a genetic template of mutations. It also should be clear from the citations presented above that mild steel welding produces a working environment rich in manganese and that without protection a career welder would be exposed to high concentrations of manganese dust and fumes in a particle size range that would result in particulate deposition in the deep lung. In addition, other components of welding fumes such as ozone and nitrogen oxides injure the defense capabilities of the pulmonary system, thereby decreasing the ability of the lung to clean itself of deep lung particulates containing manganese. Thus, the manganese oxides from welding fumes would remain in the deep lung and eventually dissolve and enter into general circulation in the blood stream either directly or via the lymphatic system and eventually find their way to the brain via an active transport mechanism. Once reaching the brain, manganese accumulates during continuing exposure and causes injury to specific tissues in the basal ganglial region of the brain, the area known to be associated with regulation of movement and organization and expression of behavior sequences. A sequella of symptoms closely resembling those of idiopathic PD follows. Manganese compounds then clear the brain after exposure ceases, but the injury caused is progressive and irreversible even in the absence of manganese.

Based on the information cited in this report and my extensive experience involving matters of toxicity and welding, I opine, within a reasonable degree of scientific certainty, that inhalation exposure to manganese from welding fumes is causally related to the development of a continuum of neurological diseases referred to as parkinsonism or Parkinson's Disease.

Since at this point in time discovery is incomplete, additional information may become available to me which will influence and perhaps alter the opinions that I have expressed in this report. In consideration of this situation, I reserve the right to supplement my report with whatever appropriate information may later become available.

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Date