



NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

Exposure of welders to manganese in welding fumes

M. Ferreira

21235988

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Supervisor: Mr PJ Laubscher

Co-supervisor: Prof JL du Plessis

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Preface

This mini dissertation is written in an article format. The article in Chapter 3 is written for the *Annals of Occupational Hygiene* therefore the references are according to their requirements. These requirements can be found at the beginning of Chapter 3 listed under the instructions to authors. For uniformity this reference style was used throughout the entire mini dissertation. Language editing was done by a competent editor (Chapter 5, Appendix A).

Author's contributions

This study was planned and executed by a team of researchers. Each researcher contributed the following:

Miss M Ferreira

- Planning and presenting the protocol of the study
- Literature research
- Respiratory sampling
- Biological sampling
- Writing of the article: Exposure of welders to manganese in welding fumes
- Interpretation of the results
- Reporting of the results
- Writing of recommendations to the industrial companies

Mr PJ Laubscher

- Supervisor
- Assistance in the planning of the study
- Authorisation of the protocol
- Feedback and recommendations regarding the study
- Reviewing of the mini dissertation and documentation of the study

Prof JL du Plessis

- Co-supervisor
- Assistance in planning and authorising the protocol
- Assistance in literature layout
- Feedback and recommendations regarding the study
- Reviewing of the mini dissertation and documentation of the study

The following is a statement from the supervisors that confirms each individual's role in the study:

I declare that I have approved the article and that my role in the study as indicated above is representative of my actual contribution and that I hereby give my consent that it may be published as part of Miriska Ferreira's M.Sc (Occupational Hygiene) mini dissertation.

Mr PJ Laubscher
(Supervisor)

Prof JL du Plessis
(Co-supervisor)

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Summary

Title: Exposure of welders to manganese in welding fumes.

Aims and objectives: The general aim of this study was to determine the personal respiratory exposure and biological monitoring of manganese (Mn) present in welding fumes as well as its neurological influence on welders. The objectives of this study were: (i) to assess the respiratory exposure of welders to Mn present in welding fumes; (ii) to assess the biological Mn load of welders via the use of nail clippings; (iii) to establish possible correlations between respiratory exposure to Mn and its presence in nail clippings, and (iv) to determine the possible difference in finger dexterity and coordination between Mn exposed welders and a control group.

Methods: A gravimetric method was used to determine the respiratory exposure of welders. A cassette containing a 0.8- μm , cellulose ester membrane filter, attached to the side of a welding helmet provided, was connected via a stainless steel fitting to the inside (respiratory zone) of the helmet. Chemical analysis (metal content) of the welding fumes was done according to the NIOSH 7300 method, using Inductively Coupled Argon Plasma, Atomic Emission Spectroscopy (ICP-AES). Nail clippings were collected at the beginning and end of the study to determine the Mn level in the nails in both welders as well as paired controls. The nails were deposited into small, plastic vials and also analysed according to the NIOSH 7300 method. A Perdue pegboard and mirror drawing test was also conducted to determine the influence of Mn exposure on finger dexterity and hand-eye coordination of welders.

Results: Mn exposure in the welding fumes did not exceed the occupational exposure limit – recommended limit (OEL-RL) (1 mg/m^3) of the Regulations for Hazardous Chemical Substances (RHCS), although two of these exposures exceeded the action level (0.5 mg/m^3). No statistical significant correlations were found between the Mn respiratory exposure and the Mn found in the nails of the welders. Mn in the nails of exposed welders was statistical significantly higher ($p = 0.003$) than that of controls. The only statistical significant differences found in the motor function tests between the controls and welders were the test which was done by using their non-dominant hand in the beginning of the study ($p = 0.016$) and when the non-dominant hand values were pooled ($p = 0.012$). The usage of both hands

simultaneously showed results that leaned toward statistical significant decrease of the welders compared to the control subjects ($p = 0.090$). In all these cases the controls inserted more pins than the welders. Only one moderately positive correlation ($r = 0.612$; $p = 0.02$) was found between Mn in the welding fumes and the number of errors made in the mirror drawing coordination test done by the welders.

Discussion and Conclusions: The Mn in the nails of the control group was significantly lower than the Mn in the nails of the welders. This indicates that Mn respiratory exposure may influence Mn body burden although no correlation between Mn in welding fumes and Mn in nails were found. Nail Mn may serve as a biomarker to determine Mn body burden. Only the use of the non-dominant hand of the control subjects compared to the welders showed a significant decrease in finger dexterity of the welders. The moderately positive association between the Mn in the welding fumes and the number of errors made in the mirror drawing coordination test done by the welders indicates that with an increase in Mn in welding fumes, a decrease in hand-eye coordination will occur. It can be concluded that welders' finger dexterity and hand-eye coordination may be influenced by the exposure to Mn in the welding fumes.

Key words: manganese, welding fumes, nail clippings, dexterity, coordination

Opsomming

Titel: Blootstelling van sweisers aan mangaan in sweisdampe.

Doelstellings en doelwitte: Die algemene doelstelling van hierdie studie was om die persoonlike respiratoriese en biologiese monitering aan mangaan (Mn) aanwesig in sweisdampe, sowel as die neurologiese invloed daarvan op sweisers, te bepaal. Die doelwitte van hierdie studie was: (i) om die respiratoriese blootstelling van sweisers aan Mn teenwoordig in sweisdampe te meet; (ii) om die biologiese Mn belading van sweisers via die gebruik van nael knipsels te meet; (iii) om moontlike korrelasies tussen respiratoriese blootstelling aan Mn en sy teenwoordigheid in nael knipsels vas te stel, en (iv) om die moontlike afwyking in vinger behendigheid en koördinasie tussen Mn blootgestelde sweisers en 'n kontrole groep, te bepaal.

Metodes: 'n Gravimetriese metode is toegepas om die respiratoriese blootstelling van sweisers te bepaal. 'n Kasset met 'n 0.8- μm , sellulose ester membraan filter was vasgeheg aan die kant van die sweishelm en is via 'n vlekvrystaal apparaat gekoppel aan die binnekant (respiratoriese sone) van die helm. 'n Chemiese analise (metaal inhoud) van die sweisdampe is onderneem volgens die NIOSH 7300 metode deur gebruik te maak van induktief gekoppelde argon plasma, atoom emissiespektroskopie. Nael knipsels is versamel aan die begin en die einde van die studie om so die Mn in die liggaam te bepaal van beide die sweisers sowel as die gepaarde kontroles. Die naels is in klein, plastiese houers geplaas en ook geanaliseer volgens die NIOSH 7300 metode. 'n *Perdue* pennetjiesbord en spieël natrektoets was ook gedoen om die invloed van Mn blootstelling op vinger behendigheid en hand-oog koördinasie van sweisers te bepaal.

Resultate: Mn blootstelling in die sweisdampe het nie die beroepsblootstellingsdrempel – aanbevole drempel (BBD-AD) (1 mg/m^3) van die Regulasies vir Gevaarlike Chemiese Substansie (RGCS) oorskry nie, alhoewel twee van hierdie blootstellings wel die aksie vlak (0.5 mg/m^3) oorskry het. Geen statisties betekenisvolle korrelasie is gevind tussen die respiratoriese blootstelling aan Mn en die Mn konsentrasie in die naels van die sweisers nie. Die Mn in die naels van die blootgestelde sweisers was statisties betekenisvol hoër ($p = 0.003$) as die van die kontroles. Die enigste statisties betekenisvolle verskille wat gevind is in die

motoriese funksie toetse tussen die kontroles en sweisers was die toets gedoen deur hul nie-dominante hand te gebruik aan die begin van die studie ($p = 0.016$) en toe die nie-dominante hand waardes saamgevoeg was ($p = 0.012$). Die gebruik van beide hande gelyktydig toon resultate wat neig na 'n statisties betekenisvolle afname vir die sweisers in vergelyking met die kontrole groep ($p = 0.090$). In al hierdie gevalle het die kontroles meer pennetjies in die bord geplaas as die sweisers. Slegs een matige positiewe korrelasie ($r = 0.612$; $p = 0.02$) was gevind tussen Mn in die sweisdampe en die aantal foute gemaak in die spieëlnatrekkoördinasie toets uitgevoer deur die sweisers.

Bespreking en Samevatting: Die Mn in die naels van die kontrole groep was betekenisvol laer as die Mn in die naels van die sweisers. Die toedrag van sake dui daarop dat respiratoriese blootstelling aan Mn die liggaamslas kan beïnvloed, alhoewel geen korrelasie tussen Mn konsentrasie in sweisdampe en Mn konsentrasie in die naels gevind is nie. Nael-Mn kan moontlik dien as 'n biomerker om Mn-liggaamslas te bepaal. Slegs die gebruik van die nie-dominante hand van die kontrole groep in vergelyking met die sweisers het 'n betekenisvolle afname in vinger behendigheid van die sweisers getoon. Die matige positiewe assosiasie tussen die Mn in die sweisdampe en die aantal foute gemaak in die spieëlnatrekkoördinasie toets onderneem deur die sweisers dui daarop dat met 'n toename in Mn in sweisdampe, 'n afname in hand-oog koördinasie sal plaasvind. Die gevolgtrekking is dus dat 'n sweiser se vinger behendigheid en hand-oog koördinasie geaffekteer kan word deur blootstelling aan Mn in sweisdampe.

Sleuteltermes: mangaan, sweisdampe, nael knipsels, behendigheid, koördinasie

List of abbreviations

ACGIH – American Conference of Governmental Industrial Hygienists
AIA – approved inspection authority
BBB – blood-brain barrier
BBD-AD – beroepsblootstellingsdrempel – aanbevole drempel
CNS – central nervous system
CSF – cerebrospinal fluid
DMT1 – divalent metal transport 1
EDTA – ethylene diamine tetra acetic acid
EEG – electroencephalogram
EPA – Environmental Protection Agency
FCAW – flux-cored arc welding
FDA – federal drug administration
Fe – iron
GMA-MS – gas metal arc-mild steel
GMAW – gas metal arc welding
LEV – Local Exhaust Ventilation
LLV – Level Limit Value
MDA - malondialdehyde
MMAD – mass median aerodynamic diameter
MMA-HS – manual metal arc-hard surfacing
MMT – Methylcyclopentadienyl manganese tricarbonyl
Mn – manganese
NIOSH – National Institute for Occupational Safety and Health
OEL – Occupational Exposure Limit
OHS – Occupational Health and Safety
OSHA – Occupational Safety and Health Administration
PAS – para-aminosalicylic acid
PD – Parkinson's disease
PEL – Permissible Exposure Limit
RGCS – Regulasies vir Gevaarlike Chemiese Substansie
RHCS – Regulations for Hazardous Chemical Substances
RL – Recommended Limit
SMAW – shielded metal arc welding
SOD – superoxide dismutase
STEL – Short Term Exposure Limit
SWEA – Swedish Work Environment Authority
TB – tuberculosis
Tf – transferrin
TLV – Threshold Limit Value
TWA – Time Weighted Average

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CHAPTER 1: GENERAL INTRODUCTION

1.1 INTRODUCTION

Manganese (Mn), an essential element which forms part of enzymes, activates other enzymes (e.g. manganese superoxide dismutase (MnSOD)), is involved in bone development, wound healing as well as in the metabolism of carbohydrates, amino acids and cholesterol (Antonini *et al.*, 2006a; Haynes *et al.*, 2012).

Mn is mainly found in the divalent (Mn^{2+}) and trivalent (Mn^{3+}) form or partially combined (Mn_3O_4) (Lidén and Surakka, 2009). Divalent Mn is the main species within cells. The more reactive and toxic trivalent form may form via the oxidation of divalent Mn (Schonwald, 2004; Liu *et al.*, 2008). Although Mn is essential for health in small quantities, it may lead to adverse health effects when exposed to in large quantities (Schonwald, 2004; Jenkins and Eagar, 2005; Liu *et al.*, 2008).

The primary source of Mn intoxication in humans can be attributed to occupational exposure to high concentrations in miners, smelters, welders and workers in dry-cell battery factories (Aschner *et al.*, 2007; Liu *et al.*, 2008). The use of Mn has expanded over time as a ferroalloy in iron (Fe) industries and as a component of alloys used in welding (Liu *et al.*, 2008). It is estimated that there are 800 000 full-time welders worldwide. The number of welders performing welding as a part of their work obligation is estimated to be between 1 and 2 million workers (Antonini *et al.*, 2003; Antonini *et al.*, 2006b).

Welding fumes have a highly variable, complex composition consisting of particles and gases (Richman *et al.*, 2011). The fumes consist of a variety of metal oxides including Mn oxides. The fume composition, concentration of various metals, and solubility of each component as well as particle size distribution depends on the site-specific properties (temperature, moisture, and air exchange) as well as method-specific properties (the type of welding process used, welding consumables, voltage and the type of electrode or wire) (Taube, 2012). Shielded manual metal arc welding (SMAW), gas metal arc welding (GMAW), and flux-cored arc welding (FCAW) constitute the common types of welding. The process of welding generates welding fumes through two steps: (1) vaporization of elements and oxides from the welding area where the electrode is consumed; and (2) rapid condensation of the vapours

forming particles (Harris, 2002; Antonini *et al.*, 2006b; Marcy and Drake, 2007; Du Plessis *et al.*, 2010).

Mn is found in all mild steels and is always used in steel alloys as it improves metallurgical properties by neutralizing the effects of sulphur and preventing molten metal oxygen contamination (Taube, 2012). In accordance with Richman *et al.* (2011) 90% of welding is performed with mild steel composed of mostly Fe and some Mn. When SMAW of mild steel is performed, it contains elevated levels of elements such as silicon, potassium and calcium in addition to Fe and Mn. If GMAW of mild steel is performed the predominant metals in the welding fumes are Fe and Mn with a mole fraction of 77-88% and 10-23%, respectively.

Mn has been associated with the development of a neurological syndrome known as chronic Mn-induced neurotoxicity or manganism; this condition elicits symptoms which resemble Parkinson's disease (Liu *et al.*, 2008; Richman *et al.*, 2011). Neurobehavioral changes have been reported in welders who were exposed to welding fumes, some case reports showing Mn accumulation in dopaminergic brain regions of welders. Normally the accumulation takes place in welders who are exposed to high welding fume concentrations although Laohaudomchok *et al.* (2011) stated that even at relatively lower airborne concentrations ($<1 \text{ mg/m}^3$) neuropsychological effects may be observed (Antonini *et al.*, 2011). Other studies found that a common exposure ($0.1 - 0.3 \text{ mg/m}^3$) to welding fumes caused adverse effects of the central nervous system (CNS) (Bowler *et al.*, 2006; Bowler *et al.*, 2007). According to several studies, neurological and neurobehavioral deficits already occur at relatively low average levels of Mn exposure ($< 0.5 \text{ mg/m}^3$). These deficits include mood changes, fine motor control and inaccurate hand-eye coordination (Bowler *et al.*, 2007; Laohaudomchok *et al.*, 2011; Taube, 2012). A study done by Wastensson *et al.* (2012) also concluded that long-term exposure to Mn resulted in adverse effects on the motor function of welders, as demonstrated by the groove pegboard test. It was however stated that this finding needs to be confirmed.

The comparison between reported epidemiological studies remains difficult due to the non-homogeneous worker populations, industrial settings, welding techniques, diverse welding materials, duration of exposure, and other occupational exposures

besides welding fumes (Antonini *et al.*, 2003; Balkhyour and Goknil, 2010; Sriram *et al.*, 2012). Other sources state that the health effects which are caused by Mn in welding fumes can also be difficult to deduce due to exposure to diverse aerosols generated from different processes and variations in workplace settings. Welders either work in a well-ventilated space (e.g., outdoors on a construction site) or in a confined, poorly ventilated space (e.g. silo) (Antonini *et al.*, 2003; Antonini *et al.*, 2006b; Antonini *et al.*, 2009; Antonini *et al.*, 2011; Sriram *et al.*, 2012).

Apart from monitoring the personal exposure to Mn, either inside the face shield or in front of the lapel/chest, biological monitoring is necessary to determine the outcome of exposure to Mn. According to Aschner *et al.* (2007), a critical matter in human Mn toxicity is the shortcoming of unfailing biological markers to determine the internal dose of Mn and its exposure to the welders. Winder (2004) as well as Gil *et al.* (2011) stated that biomonitoring of exposure to heavy metals, such as Mn in occupational toxicology, is widely done via blood and urine samples, although blood Mn does not serve as a reliable indicator of the total body burden of Mn or of the overall disease status; this is due to intracellular distribution and relatively short half-life of Mn in the blood compartment. Urine Mn is even less likely to be a clinical indicator for Mn toxicity due to the fact that Mn excretion (> 95%) is via bile to faeces (Gil *et al.*, 2011). For that reason Aschner *et al.* (2007) stated that there is no reliable biomarker to clinically assess the degree of Mn neurotoxicity and it is therefore necessary to consider the patient's occupational history.

A recent study done by Sriram *et al.* (2012) found that the sulphur rich keratin forming part of the nail has a high affinity for metal cations such as Mn. Nail clippings can therefore be a reliable matrix for evaluating metal toxicity, especially in the case of Mn. Studies detected several drugs in nail clippings as early as one or two weeks after administration. The presence of a drug in nail clippings can therefore result from consumption of the drug recently or in the remote past (Matthieu *et al.*, 1991; Willemsen *et al.*, 1992; Schatz *et al.*, 1995; Faergemann and Laufen, 1996). The drug can be incorporated into the nail plate from the nail bed even to the most distal segment of the nail bed, close to the site of nail clipping. Diffusion through the nail plate is the primary route of penetration (Palmeri *et al.*, 2000).

The Perdue pegboard test is considered to be an easy assessment which can be applied to measure the upper extremity fine motor dexterity of welders exposed to Mn (Gallus and Mathiowetz, 2003; Tiffin, 2008). The mirror drawing test is defined as an assessment which can be used to determine coordination of welders exposed to Mn in welding fumes (Midorikawa *et al.*, 2008).

In light of the above, it should be clear why the use of nail clippings as a biomarker and the performance of the Perdue pegboard and mirror drawing tests are the most reliable indicators to determine the exposure of welders to Mn in welding fumes, as well as to substantiate previous literature regarding Mn toxicity.

1.2 RESEARCH AIMS AND OBJECTIVES

The general aim of this study is to determine the personal respiratory exposure and biological monitoring of Mn present in welding fumes as well as its neurological influence on welders.

The following objectives:

1. to assess the respiratory exposure of welders to Mn present in welding fumes;
2. to assess the biological Mn load of welders via the use of nail clippings;
3. to establish possible correlations between respiratory exposure to Mn and its presence in nail clippings; and
4. to determine the possible difference in finger dexterity and coordination between Mn exposed welders and a control group.

1.3 HYPOTHESIS

The following hypothesis is postulated:

Since occupational exposure to Mn in welding fumes is a serious occupational health problem all over the world it is important to find an effective, inexpensive and reliable indication of Mn body burden. It is therefore hypothesized that there is a statistical significant correlation between the Mn respiratory exposure and the body burden of Mn found in nails of the welders as well as a significant decrease in finger dexterity and coordination of the welders compared to the control group.

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CHAPTER 2: LITERATURE STUDY

In this chapter, published literature regarding manganese (Mn) in welding fumes will be critically discussed. An overview of Mn followed by its involvement in the welding processes will be supplied. This will be followed by a complete discussion of the toxicology and consequences of toxicity of Mn in welding fumes. Finally, strategies regarding monitoring of exposure and treatment for Mn toxicity will be elaborated upon.

2.1 MANGANESE

Mn is a trace element and is an essential metal required for many metabolic and cellular functions; it can be found in rock, soil, food and water. It is also essential for normal development and body function of mammals. Mn acts as a cofactor in many enzymatic reactions which involve bone mineralization, protein and energy metabolism, metabolic regulation, protection from free radical species and the formation of glycosaminoglycans. Mn metalloenzymes include arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase and manganese superoxide dismutase (MnSOD) (Schonwald, 2004; Liu *et al.*, 2008; Santamaria and Sulsky, 2010; Taube, 2012; Wastensson *et al.*, 2012).

2.1.1 Categories and uses

There are three categories of Mn: (i) *metallic Mn*, which is used in steel production to improve hardness, stiffness and strength and it is used to make various steels, cast iron and super alloys; (ii) *inorganic Mn*, which include manganese chloride (MnCl_2), manganese sulphate (MnSO_4), manganese phosphate (MnPO_4), manganese oxide (MnO_2) and manganese tetraoxide (Mn_3O_4); and (iii) *organic Mn compounds* such as methylcyclopentadienyl and manganese tricarbonyl, which is used as a fuel oil additive and a smoke inhibitor (Schonwald, 2004; Liu *et al.*, 2008). More than 90% of mined Mn gets utilized for the production of steel (Bowler *et al.*, 2006).

2.1.2 Properties

Mn is a transition metal consisting of multiple species including Mn^{2+} , Mn^{3+} and Mn^{4+} which are all observed in the fume generated during welding. The proportions of the

different Mn species vary in relation to the process and settings of welding (Antonini *et al.*, 2003; Antonini *et al.*, 2011). Mn is a critical element in the welding of steel and is found in consumable welding in various concentrations. It is used to increase hardness and strength, prevent steel from cracking during manufacturing, improve the metallurgical properties while also acting as a deoxidizing agent to form a stable weld by removing iron oxide from the weld pool (Harris, 2002; Antonini *et al.*, 2006a; Antonini *et al.*, 2006b). Mn has an atomic mass of 54.94 and a density of 7.21 – 7.44 depending on the allotropic form. Its melting point is 1244 °C and boiling point 1962 °C (Gerber *et al.*, 2002). According to Lidén and Surakka (2009), the element's low boiling point in comparison to that of iron (Fe) (2750 °C) is the reason why it is 4 to 6 times more abundant in the fume of welding processes than in the filler material binding the two surfaces.

2.2 WELDING

Welding is a common industrial process where heat is applied to a specific area to join two or more metal parts. Melting of metals occurs as a result of heat, and after cooling the heat creates a strong connection between the metal parts. Throughout a welding process, small metal particles (or better known as welding fumes) and gases are released. The welding fumes contain a mixture of metallic oxides, fluorides and silicates while the gases known as shielding gas mixture, contain argon, helium, carbon dioxide and oxygen. They are used to establish a stable arc, obtain a smooth molten metal transfer and to reduce fume emissions. This shielding gas also produces toxic gases such as nitrogen oxide and ozone. In the welding fumes a complex array of metals, metal oxides and other chemical species volatilize from the welding electrode or the flux material incorporated within the electrode. These metals include Mn, Fe, silicon, chromium, nickel, copper, potassium and calcium of which the primary component is iron oxide. A small percentage of Mn together with other metals appears in most welding fumes. The amount of Mn released in the fumes varies according to the type of welding process as well as the amount of Mn in the welding fire, rods or electrode and base metal used (Antonini *et al.*, 2003; Antonini *et al.*, 2006a; Antonini *et al.*, 2006b; Aschner *et al.*, 2007; Pires *et al.*, 2007; Dasch and D'Arcy, 2008; Antonini *et al.*, 2009; Du Plessis *et al.*, 2010; Brown 2012; Hoet *et al.*, 2012; Lehnert *et al.*, 2012).

2.2.1 The process

According to Bowler *et al.* (2006), there are approximately 80 different types of welding processes utilized in manufacturing. The three common welding processes are associated with elevated fume exposure: a) shielded metal arc welding (SMAW) also known as “stick welding” which is a manual, simple, inexpensive process and very often used in construction, b) gas metal arc welding (GMAW) which is an automatic welding process that utilizes a welding gun that automatically feeds the weld metal through the gun, widely used in automobile repair and manufacturing, c) flux-cored arc welding (FCAW) also an alternative “stick welding” used in automatic, fast-speed applications (Brown, 2012). SMAW and FCAW incorporate fluxing compounds into the electrode. A shielding environment forms to protect the weld while the electrode is consumed during the welding process. The fluxing agents used during these two processes contribute to respiratory exposure of welders. The fume is also classified as chemically and physically more complex than the fume formed during the third process GMAW (Zimmer and Biswas, 2001; Jenkins and Eagar, 2005; Antonini *et al.*, 2006a; Antonini *et al.*, 2006b). According to Antonini *et al.* (2003) and Antonini *et al.* (2006b), x-ray photoelectron spectroscopy and x-ray diffraction show that the most probable oxidation states of Mn in welding fumes are Mn^{2+} and Mn^{3+} (existing as MnO and Mn_2O_3), usually generated from both GMAW and SMAW processes.

GMAW, also known as *metal inert gas* or MIG welding, is a semiautomatic or automatic process making use of an incessant wire supply as an electrode and an inert or semi-inert gas mixture. It is also one of the most common types of welding in the industry, ascribed to the fact that it continually blows shielding gases over the arc, protecting the weld from deterioration caused by oxidation. The formation of fume occurs due to the vaporisation of the metals. The volatilization takes place at the tip of the electrode, where the electric arc occurs. The electrode wire consumed during the welding process is the primary origin of the majority of the fumes. The formed welding fumes is the vaporized metal coming into contact with air causing oxidation to occur (Antonini *et al.*, 2003; Antonini *et al.*, 2006a; Antonini *et al.*, 2006b; Du Plessis *et al.*, 2010; Antonini *et al.*, 2011). This oxidation results in particle formation, primarily of respirable size, composed of a complex mixture of metal

oxides (Harris *et al.*, 2005; Lehnert *et al.*, 2012; Pesch *et al.*, 2012). The process, process variables, current level and composition of the wire/flux used during welding determine the type and quantity of the welding fumes produced. The larger the current levels are, the higher the fume rate becomes (Antonini *et al.*, 2003; Antonini *et al.*, 2011). Also depending on the welding process and the composition of the welding electrode, are the different oxidation states and different solubility properties Mn may occur in. The biological responses to Mn after inhaling welding fumes may be affected by these differences (Antonini *et al.*, 2003; Antonini *et al.*, 2006a; Antonini *et al.*, 2006b).

2.2.2 Size distribution of welding fumes

A study conducted by Lidén and Surakka (2009) revealed that the inhalable portion of welding aerosol mass consisted of 25 – 55 % welding fumes. The remainder was welding spatter, grinding dust and slagging dust. It was concluded that more than 65% of the Mn found was part of the fume particles. The particle size distribution of welding aerosols is generated by a welder either performing welding or grinding consisting of different modes. The smallest mode consists of a mass median aerodynamic diameter (MMAD) usually < 1 µm and occur due to condensation of volatilized metals (Dasch and D'Arcy, 2008; Ellingsen *et al.*, 2008; Lidén and Surakka, 2009). In a study done by Brand *et al.* (2012) it was found that any manual metal arc welding technique exclusively consists of particles between 60 – 200 nm with a high mass emission rate and that only a small fraction of particles have a diameter < 50 nm (low mass emission rate), while Antonini *et al.* (2006b) stated that aerosols generated from GMAW alloy aerosols were 149 nm while FCAW aerosols were even larger (352 nm). According to Jenkins and Eagar (2005), less than 10 – 30 % of fume mass is larger than 1 µm but it depends on the welding process used. The largest size mode are particles > 20 µm and occur during metal expulsions or spatter (Dasch and D'Arcy, 2008; Lidén and Surakka, 2009). These particles are 'spherical' and consist of solid molten metal droplets which are ejected out of the weld and contain a high fraction of non-oxidized metals (Lidén and Surakka, 2009).

According to Laohaudomchok *et al.* (2011), 90 % of the mass from welding emissions occurs in the respirable range of which over 80 % consists of particles smaller than 1 µm. Analyses using electron microscopy confirmed that the primary

particles generated during welding are in the nano-size range (0.01 – 0.10 µm). Although released as nanoparticles, these particles rapidly agglomerate together in the air to form longer chains of primary particles with an aerodynamic diameter in the range of 0.1 – 0.6 µm (Antonini *et al.*, 2003; Antonini *et al.*, 2006b; Brand *et al.*, 2012). The agglomeration of particles may in addition be influenced by factors such as temperature, humidity and air motion (Lehnert *et al.*, 2012). These particles, of which Mn is part of, can easily be absorbed into the blood subsequent to reaching the alveolar or pulmonary region of the respiratory tract after inhalation occurred (Antonini *et al.*, 2006b; Dorman *et al.*, 2006).

2.2.3 Deposition of welding fumes

The potential health impact associated with inhalation of welding fumes consisting of the appropriate metals innate to the welding process, depends on the site where the particles deposit in the respiratory tract, as well as how the particles will be cleared from the lungs (Antonini *et al.*, 2006b). The uptake of particles by the respiratory tract is chronological, causing particles to move from the nasal/oral boundary through the respiratory system. The particles come into contact with the respiratory tract and move through the layers of the respiratory tract where it reaches the bloodstream or lymphatic system. Each layer, through which the particles move, provides a form of resistance to particle transport (Ferro and Hildemann, 2007; Pośniak and Skowroń, 2010).

The respiratory tract is divided into three major regions. The first region, known as the *nasal-pharyngeal* or *extra-thoracic* region, includes the nasal passages, the pharynx and the larynx. The function of this region is to warm and moisten the inhaled air and to filter out coarse particulate matter larger than 5 µm in the complex airflow patterns of its passages (Antonini *et al.*, 2006b; Ferro and Hildemann, 2007; Pośniak and Skowroń, 2010). These particles are known as the inhalable fraction, including thoracic and respirable fractions defined as “the mass fraction of total airborne particles that are inhaled through the nose and/or mouth” (Cherrie *et al.*, 2010). The second region, namely the *trachea-bronchial* or *thoracic* region, includes the trachea, bronchi and bronchioles. First-mentioned branches into the left and right main bronchi. These bronchi lead to the left and right lung. The main bronchi thereafter branches into gradually more smaller-in-diameter-and-length bronchi and

bronchioles. Particles in this region have an aerodynamic diameter of 2-5 μm and can easily access the bloodstream (Antonini *et al.*, 2006b; Ferro and Hildemann, 2007; Pośniak and Skowroń, 2010). These particles are known as the thoracic fractions which includes respirable fraction, and is defined as “the mass fraction that penetrates the respiratory system beyond the larynx” (Cherrie *et al.*, 2010).

The second region subdivides the airway to reach the third region, known as the *alveolar, pulmonary or gas exchange* region. The latter region, where gaseous exchange takes place, includes partially alveolated respiratory bronchioles, alveolar ducts and alveoli. The alveoli are seen as tiny sacs which have an enormous surface area which facilitate gaseous exchange with the bloodstream. Particles with a diameter of less than 1 μm will be present in this region (Antonini *et al.*, 2006b; Ferro and Hildemann, 2007; Cherrie *et al.*, 2010; Pośniak and Skowroń, 2010). These particles are known as the respirable fraction and are defined as “the mass fraction that penetrates to the unciliated airways of the lung, known as the alveolar region, where the gas exchange takes place” (Cherrie *et al.*, 2010). Welding particles with a diameter of 0.5 – 2.0 μm have been observed in a welder’s breathing zone, increasing the probability of depositing into the lower respiratory tract (Antonini *et al.*, 2003; Antonini *et al.*, 2006b).

Welding particles, both soluble and non-soluble forms of metal which deposit in the nasal-pharyngeal region, can lead to direct transfer from the nose to the brain via olfactory transport, bypassing the first-pass hepatic clearance. While this transport occurs, another bypass at the blood-brain barrier may take place causing inhaled metals such as manganese, cadmium, nickel and mercury to be transmitted along cell processes to synaptic junctions with olfactory bulb neurons (Tjälve and Henriksson, 1999; Beuter *et al.*, 2004; Dorman *et al.*, 2004; Antonini *et al.*, 2006b; Liu *et al.*, 2008; Antonini *et al.*, 2009). Mn is able to cross synapses within the olfactory pathway and it uses secondary and tertiary neurons to travel to other distal sites in the brain, including the hypothalamus (Tjälve *et al.*, 1995; Dorman *et al.*, 2006; Elder *et al.*, 2006).

According to Fechter *et al.* (2002), being exposed to non-soluble MnO_2 aerosols with a MMAD of 1.3 μm for 3-weeks via the nose result in significant Mn concentration increases in the olfactory bulb. A number of rat studies done by Antonini *et al.*

(2006b) also proved that inhaled particles ranging between 0.1 and 0.6 μm reach the brain via olfactory transport. Particles (within the size range of $< 2 \mu\text{m}$) deposited on the olfactory mucosa will be directly transported through the cribriform plate (a horizontal bone plate which consist of several holes for the passage of olfactory nerve filaments) to the olfactory bulb and does not use any extrapulmonary translocation (Elder *et al.*, 2006; Antonini *et al.* 2009).

2.2.4 Clearance of welding particles

Different methods of clearing welding particles from the nasal-pharyngeal airway, tracheo-bronchial and the alveolar region occur. Welding particles deposited in the tracheo-bronchial region will be removed by the mucocilliary escalator. During the inhalation of particles into this region, a layer of mucus causes an entrapment. Ciliary movement carries the particles up the mucociliary escalator to the mouth where it then gets swallowed, processed and excreted via the gastrointestinal tract. Mn is highly unlikely to be reabsorbed back into the body due to the fact that it has a fast elimination time, the majority of welding particles are insoluble and there is a limited rate of gastrointestinal Mn absorption (McClellan, 2000). According to Richman *et al.* (2011), reduction of toxicity in the nervous system may occur due to clearing Mn from the pulmonary system with the mucociliary escalator. Engulfing particles by alveolar macrophages may also occur. Whenever particles reach the alveolar region the particles will be phagocytised by macrophages and remain there for extended periods of time. Non-toxic particles may remain there for up to 700 days in humans. After the mucociliary escalator cleared the particles from the respiratory tract, it is possible that some particles may remain. These particles may be transferred to interstitial spaces via macrophages and other phagocytic cells (e.g. neutrophils) or through the lymphatic system to lung-associated lymph nodes. Some particles may also gain direct uptake via alveolar type I cells, lining the epithelium of alveoli. These particles will be transported from the alveolar space directly to the bloodstream due to a very short distance (approximately 0.5 μm) between the alveolar space and the pulmonary capillary (McClellan, 2000; Oberdörster, 2004; Antonini *et al.*, 2009). The lung epithelium does not only serve as a passive barrier but also plays an important role in secreting inflammatory cytokines in response to toxic stress (Pascal and Tessier, 2004). The ultrafine particles causing toxic stress

have an increased probability to escape phagocytosis in the lungs and end up in the systemic circulation, and subsequently other organ systems (Antonini *et al*, 2009).

2.3 TOXICOLOGY

2.3.1 General toxicity

Welding fumes contain a variety of elements in its untainted forms which can be hazardous when inhaled or ingested by the worker (Jenkins and Eagar, 2005; Taube, 2012). These welding fumes can enter the lungs, bloodstream, brain nerve cells, spinal cord and other organs causing both short and long term health effects (Balkhyour and Goknil, 2010). It is therefore of critical importance to examine the chemical composition of welding fumes when studying fume toxicity. Forming part of these welding fumes is Mn. Although essential for health in small quantities, it is a neurotoxin which may cause Mn poisoning when exposed to in large quantities (Jenkins and Eagar, 2005; Taube, 2012).

2.3.2 Toxicokinetics

Regardless of Mn intake, adults normally maintain stable tissue Mn levels. This occurs due to regulation of absorption and excretion (Schonwald, 2004; Liu *et al.*, 2008). Mechanisms which transport and store Mn exist whereas non-essential elements do not have these mechanisms (Antonini *et al.*, 2006b). The human body contains approximately 10 mg of Mn, which is stored mainly in the liver and kidneys (Schonwald, 2004; Liu *et al.*, 2008).

Approximately 1 – 5 % of ingested Mn is absorbed overall. Absorption of Mn from the GI tract is age dependent with older individuals having a lower absorption rate than that of neonates. The toxicokinetics of Mn is complicated by the interaction between Mn and Fe, as well as other divalent elements, especially via oral exposure. A risk factor of Fe deficiency arises due to an increase in the amount of Mn absorbed from the GI tract causing an enhancement of Mn to the brain although brain delivery is enhanced rather by inhalation than ingestion of Mn. The absorption of this element after inhalation results in arrival at tissue stores and has a slower turnover compared to when orally absorbed. Mn, in general, is found in human tissue, blood,

serum and urine (Schonwald, 2004; Antonini *et al.*, 2006b; Dorman *et al.*, 2006; Teeguarden *et al.*, 2007; Aschner *et al.*, 2007; Liu *et al.*, 2008).

Tissue distribution of Mn usually reflects chronic and not acute exposure. Tissue having the most mitochondria, such as the liver, pancreas, kidneys and intestines, contain the highest concentration of Mn due to the fact that this element accumulates in mitochondria. The main route of Mn excretion is via bile (80 %), after which it is reabsorbed in the intestine and then excreted via faeces, even though some excretion occurs in urine, milk and sweat (Schonwald, 2004; Antonini *et al.*, 2006b; Dorman *et al.*, 2006; Aschner *et al.*, 2007; Liu *et al.*, 2008). Gerber *et al.* (2002) stated that the half-life Mn elimination is approximately 37-39 days in controls and are less in Mn exposed workers.

2.3.3 Manganese transport in the central nervous system

Mn enters the brain via the systemic circulation. The Mn either crosses the cerebral capillaries and/or the cerebrospinal fluid (CSF). When the plasma concentrations are normal, Mn transports into the CNS across the capillary endothelium while when the plasma concentrations are high it crosses the choroid plexus. With rapid appearance and persistent increase of Mn in this organ, transport across the choroid plexus dominates. Mn crosses the blood-brain barrier (BBB) and accumulates in explicit brain regions. The following mechanisms are involved in transporting Mn across the BBB: facilitated diffusion, active transport, divalent metal transport one (DMT1) – mediated transport, ZIP8- and transferrin (Tf) – dependent transport (Aschner *et al.*, 2007). According to Haynes *et al.* (2012), inhaled Mn can persist in the lungs and has the ability to enter the systemic circulation directly through bypassing the biliary excretion mechanism. This will cause direct transfer to the CNS (Antonini *et al.*, 2006b).

Although divalent Mn²⁺ shows a relative low affinity for endogenous ligands, the Mn can be taken up by neurons, oligodendrocytes and astrocytes for usage and storage (Aschner *et al.*, 2007). Consistent with Antonini *et al.* (2009) short term inhalation of Mn in welding fumes cause a significant increase in DMT1 expression in the striatum and midbrain implying that the Tf receptors and DMT1 are the major transporters for Mn (Aschner *et al.*, 2007).

2.4 CONSEQUENCES OF TOXICITY

2.4.1 Exposure to manganese

2.4.1.1 Environmental exposure

Metallurgic and chemical industries, burning coal and petrol containing methylcyclopentadienyl manganese tricarbonyl (MMT), contribute to the discharge of Mn into the environment (Gerber *et al.*, 2002). Mn based organometallic pesticides, maneb and macozeb, may often also lead to environmental exposure (Liu *et al.*, 2008). According to Gil *et al.* (2011), certain heavy metal exposures pose a risk for accumulating in the environment which may bring about accumulation in living organisms and cause toxicity. The atmospheric Mn concentrations may vary from less than 0.0001 – 0.01 mg/m³ depending on the distance from Fe, steel or alloy plants (Gerber *et al.*, 2002). According to Dorman *et al.* (2006), Mn inhalation experienced by non-occupational persons in the environment are only a small fraction (<0.1 %) of the total Mn intake. Mn is therefore no threat in the environment, though small traces of Mn sometimes occur in soil. This unthreatening situation will occur on the condition that high Mn concentrations are not inhaled or ingested via contaminated water (Gerber *et al.*, 2002).

2.4.1.2 Consumer exposure

According to Gerber *et al.* (2002) and the Environmental Protection Agency (EPA, 2012a), the human body contains approximately 10 mg Mn, having a 5 – 8 mg Mn turnover on a daily basis. The daily food consumption varies between 5.4 and 12.4 mg while a daily intake of 2 – 3 mg/day was considered being adequate for adults. It was concluded that an appropriate dose for Mn is 10 mg/day (0.14 mg/kg-day) (EPA, 2012a). The ingestion of contaminated water has been documented to cause Mn intoxication (Liu *et al.*, 2008). In the US it was concluded that the standard for Mn in drinking water is 0.05 mg/L (EPA, 2012b). No toxicity will therefore occur from Mn containing food or from taking reasonable amounts in supplements (Gerber *et al.*, 2002). According to Dorman *et al.* (2006), individuals with suboptimal Mn intake stand a chance to increase the risk of Mn toxicity in the workplace.

2.4.1.3 Occupational exposure

Mn intoxication was initially described by Couper (1837) who noticed that workers developed changes in speech and way of walking due to inhalation of Mn oxides coming from the grinding process of pyrolusite ore (MnO₂). The primary source of Mn intoxication in humans is due to occupational exposure to high concentrations of Mn in miners, smelters, welders, workers in dry-cell battery factories and working with fertilizers and fungicides containing Mn (Bowler *et al.*, 2006; Dorman *et al.*, 2006; Aschner *et al.*, 2007; Liu *et al.*, 2008). The welding industry emits an estimation of 5000 tons of welding fumes per year worldwide (Redding, 2002). Complex metal particles may occur in these fumes causing health effects after inhalation exposure (Antonini *et al.*, 2011). The respiratory exposure of welders varies in relation to materials used and differences in welding processes. SMAW, GMAW and FCAW are the most common industrial methods (Taube, 2012). During arc welding occupational exposure to high concentrations of Mn oxide-containing ultrafine particles takes place (Elder *et al.*, 2006).

2.4.2 Occupational exposure limits for manganese in welding fumes

The ACGIH first adopted a health-based TLV-TWA of 200 mg/m³ for inorganic Mn compounds or total dust due to the caution of CNS impairment. During that time respirable and non-respirable particles were indistinct (ACGIH, 1995). After noticing the impact of these particles on the health of welders, it was listed as a limit to be changed in accordance to fraction size and was proposed at 0.2 mg/m³ for Mn in the respirable fraction. This limit is still in use today (ACGIH 2012).

Table 1: Different occupational exposure limits for Mn as a fume			
	Country	TWA	STEL
RHCS[§]	South Africa	1 mg/m ³ OEL-RL	3 mg/m ³ STEL-RL
NIOSH – REL (NIOSH, 2010)	USA	1 mg/m ³	3 mg/m ³
ACGIH – TLV (ACGIH, 2012)	USA	*0.2 mg/m ³	
OSHA – PEL (OSHA, 2012b)	USA	5 mg/m ³ ceiling	
SWEA – LLV (SWEA, 2005)	Sweden	#0.2 mg/m ³ total dust #0.1 mg/m ³ respirable dust	

[§] Regulations for Hazardous Chemical Substances, 1995 under the Occupational Health and Safety Act (Act 85 of 1993)

* TLV listed as manganese and inorganic compounds, as Mn

LLV listed as manganese and inorganic compounds, as Mn

2.4.3 Health effects and symptoms

2.4.3.1 Neurotoxicity

Neurotoxicity can occur after high Mn levels are orally administered, inhaled, paternally exposed or when hepatobiliary clearance is impaired (Dorman *et al.*, 2006). The different valence states of Mn have the capacity to promote redox reactions and form cytotoxic free radicals which will affect the health of exposed welders (Antonini *et al.*, 2003). Mn neurotoxicity was initially identified as an extra-pyramidal syndrome in miners which were exposed to high concentrations of Mn ore (Aschner *et al.*, 2007). Mn has been known to be a neurotoxicant for at least 150 years (Bowler *et al.*, 2006; Aschner *et al.*, 2007). The brain is considered the most susceptible organ to Mn (Liu *et al.*, 2008). Inhalation of pure Mn in high doses may cause neurological effects, however in welding fumes it is not present as a pure element. The fume consists of a composition of metals, and may not create the same health effects as pure Mn (Antonini *et al.*, 2006a). The amount of Mn fume present in welding processes and materials during occupational exposure was determined by an epidemiologic study to be in the region of 0.01 – 5 mg/m³ (Li *et al.*, 2004).

Early manifestations of Mn neurotoxicity include headache, fatigue, insomnia, memory loss, muscle cramps, change in appetite and emotional unsteadiness (behavioural changes). Preliminary external symptoms develop step by step and are mainly psychological (i.e., depression, agitation, hallucinations). Cognitive discrepancies such as memory impairment, reduced learning capacity, decreased mental flexibility, cognitive slowing and difficulty with visuomotor and visuospatial information processing has been reported. Slightly inferior as well as severe impaired motor functions have also been reported (Bowler *et al.*, 2006; Aschner *et al.*, 2007; Ellingsen *et al.*, 2008; Liu *et al.*, 2008; Chang *et al.*, 2009). A neurophysiological study done by He and Niu (2004) on welders exposed to Mn which included an electroencephalogram (EEG) established that these exposed welders have increased theta and delta wave activity in relation to controls. This increase of activity is likely an indication of depression or fatigue. Without treatment the above mentioned symptoms more often than not progress (Aschner *et al.*, 2007).

With continuing Mn exposure and disease progression, patients may develop a long-lasting motor disorder or better known as parkinson's symptoms such as muscle contractions (dystonia) and/or ataxia, bradykinesia, decreased muscle movement (hypokinesia), rigidity, hand tremor, speech disturbances, postural instability, and festinating "cock-walk" gait (Dorman *et al.*, 2006; Aschner *et al.*, 2007; Liu *et al.*, 2008). In rigorous situations, patients may present tremors at the angle of the lips and at the tip of the tongue; this may lead to tongue biting while speaking. These patients' handwriting also becomes characteristically uneven, specifically battling to draw circles, and decreasing the size of letters. It is said that patients with Mn intoxication battle to simply cope with life (Aschner *et al.*, 2007). The above mentioned signs are associated with dopaminergic neuron damage which is responsible for muscle movement control (Liu *et al.*, 2008). Results became more obvious in the twentieth century and it was stated that generalizing on the outcome of exposure duration on neurotoxicity was difficult, given the different Mn salts and species used to experiment (Aschner *et al.*, 2007). Neurotoxicity was reported in a number of occupational settings causing neurobehavioral impairment due to inhalation of airborne Mn ranging from 0.027 to 1 mg/m³ (Lucchini *et al.*, 1999; Liu *et al.*, 2008). A study done by Roels *et al.* (1992) revealed adverse health effects at levels as low as 0.15 mg/m³. Bowler *et al.* (2007) conducted a study on welders exposed to relatively low average levels of Mn (< 0.5 mg/m³) and found that neurological and neurobehavioral deficits do occur. Mood changes, short-term memory loss, prolonged reaction time and an influence in accurate hand-eye coordination was detected in this study. Another study stated that these above mentioned deficits may even occur at levels as low as 0.2 mg/m³ (Taube, 2012). A study undertaken by Laohaudomchok *et al.* (2011) also proved that even at relatively low airborne concentrations of Mn in welding fumes (0.004 – 0.137 mg/m³), neuropsychological effects may occur particularly with respect to attention, mood, and fine motor control. Takeda (2003) confirmed that neurological disorders similar to Parkinson's disease occur once there is an abnormally high concentration of Mn in the brain especially in the basal ganglia. The basal ganglia fit in to a complex neural network engaged in the creation of tremors.

2.4.3.1.1 Manganism and Parkinson's disease (PD)

Manganism is a critical condition which is associated with exposure to extreme Mn levels which will cause high levels of Mn in the brain, especially in the areas where high concentration levels of non-heme Fe occur, such as the substantia nigra, basal ganglia, caudate putamen, globus pallidus, and subthalamic nuclei (Beuter *et al.*, 2004; Li *et al.*, 2004; Aschner *et al.*, 2007; Perl and Olanow 2007; Ellingsen *et al.*, 2008; Liu *et al.*, 2008; Santamaria and Sulsky, 2010). Manganism has been reported in workers employed by mines and crushing of Mn ore, Mn alloy production and in the production of steel and dry cell batteries (Ellingsen *et al.*, 2008).

Crossgrove and Zheng (2004) as well as Jiang *et al.* (2006) stated that manganism may occur more consistent in smelters than in welders, most likely because welders have a variation of jobs from day-to-day and are inconsistently exposed to the welding fumes containing Mn. Another statement was made that manganism diagnosis is less ambiguous for currently working patients than for patients who left the job long ago. Manganism is developing at a younger age, being observed in young workers although it may manifest years after exposure or only after the worker retires (Winder, 2004; Bowler *et al.*, 2006). According to Dorman *et al.* (2006), aged individuals in the workplace have an increased risk for developing Mn toxicity. Results from an animal study (Erikson *et al.*, 2004) indicated that age may be an important variable and needs to be considered during assessment of occupational Mn neurotoxicity. According to Chu *et al.* (2002), Mn exposure may influence the aged nervous system negatively. People aged 60 – 80 years' experience a loss of 50% functional reserve dopaminergic neurons although a study done by Li *et al.* (2004) observed that younger welders (≤ 30 years), with less professional years had a higher serum Mn level (0.39 $\mu\text{g}/\text{dL}$) than older welders (31 – 40 years; average 0.26 $\mu\text{g}/\text{dL}$), and may experience adverse health effects sooner. Motivation for this higher serum Mn levels in the younger workers may be due to physiological factors (faster breath rate and more dynamic cardiac function), physical activity (younger welders work longer hours) or inexperience (unsafe work practice). Differences in toxicokinetics among different age groups as well as variations in biochemical parameters (plasma protein binding) may also contribute to higher levels of Mn in serum (Li *et al.*, 2004).

Manganism is a neurological syndrome regarded as a CNS abnormality and neuropsychiatric disturbance and is said to be similar to PD (Antonini *et al.*, 2006a; Antonini *et al.*, 2006b; Ellingsen *et al.*, 2008). There are three different stages of manganism characterized, namely: (1) the prodromal phase, dominated mostly by subjective symptoms; (2) the intermediate phase where various neurological signs appear; and (3) the established phase where severe disabling neurological signs appear (Ellingsen *et al.*, 2008). PD, also known as *paralysis agitans*, arises from extensive damage to a certain part of the substantia nigra which is responsible for sending dopamine-secreting nerve fibers to the caudate nucleus and putamen. Dopamine is an inhibitory transmitter secreted in the caudate nucleus and putamen. Damage to the dopaminergic neurons in the substantia nigra causes the caudate nucleus and putamen to become overly active which result in continuous output of excitatory signals to the corticospinal motor control system (Antonini *et al.*, 2006b; Guyton and Hall, 2010).

Table 2: Similarities and differences in symptoms between manganism and PD	
(Facca and Koller, 2003; Beuter <i>et al.</i> , 2004; Schonwald, 2004; Winder, 2004; Antonini <i>et al.</i> , 2006a; Antonini <i>et al.</i> , 2006b; Bowler <i>et al.</i> , 2006; Aschner <i>et al.</i> , 2007; Ellingsen <i>et al.</i> , 2008; Antonini <i>et al.</i> , 2009; Guyton and Hall, 2010)	
Similarities	
<ul style="list-style-type: none"> • Cause general bradykinesia • Widespread rigidity occur • Is seen as a dysfunction in the basal ganglia 	
Manganism	PD
Internal differences	
<ul style="list-style-type: none"> • Substantia nigra not affected • Mainly target the globus pallidus and the striatum of the basal ganglia 	<ul style="list-style-type: none"> • Loss of dopaminergic neurons in the substantia nigra • Neurdegeneration takes place in the substantia nigra
Visible differences	
<ul style="list-style-type: none"> • Has the following feature: neurological, psychological, apathy, confusion, bizarre behaviour, increased muscle tone, difficult speech and loss of balance; • Psychiatric disturbances occur early; • Patients have a tendency to fall back when pushed; have less frequent resting tremor, more frequent dystonia, a cock walk, and may often fail to respond to dopaminergic agonists; • Neurodegenerative disorders have a frequent resting tremor of 4 to 6 Hz; • Headaches appear more common. 	<ul style="list-style-type: none"> • Many or even all of the bodies' muscles will become overly excited, thus causing rigidity; • Dementing normally occurs late; • Normal physiological tremor has a frequency that range between 7 and 12 Hz; • Headaches are uncommon.

In accordance with Racette *et al.* (2001), studies conducted on humans showed that chronic exposure to Mn in a selection of occupations may elevate the risk of obtaining or accelerating PD. Park *et al.* (2005) also stated that welders are at an increased risk for developing neurodegenerative diseases. According to Antonini *et al.* (2006b), welding may also be a possible risk factor for developing PD. The increased risk of developing PD due to low levels of Mn exposure in sensitive populations has also been confirmed by Lucchini *et al.* (2009). The acceleration of neurotoxic conditions such as PD development resulting from low level Mn exposure has also been established by Martin (2006). According to Ono *et al.* (2002), a 17-year old electric arc welder showed myoclonic involuntary movement of the right upper and lower extremities due to chronic Mn poisoning, but no PD. The MRI showed Mn accumulation in the brain. Another study (Goldman *et al.*, 2005) revealed that welding did not increase the risk of developing PD. Foreed *et al.* (2006), used a nationwide cohort of Swedish welders and also found no correlation between welding and PD or any other movement disorders. Another study conducted determined a continuum of changes between tremors recorded in control subjects, Mn exposed subjects and PD patients with the Mn -group always resorting in between the control group and the PD group. The blood Mn levels were back to the levels conducted in control groups, but postural tremors were still detected due to Mn exposure (Beuter *et al.*, 2004). No conclusion can therefore be made as to whether or not Mn exposure to career welders will cause PD. The only convincing diagnosis is that of manganism when welders are chronically exposed to the element. Mn toxicity usually reflects that of chronic exposure and not of acute exposure, although metal fume fever (MFF) may result from acute Mn fume inhalation (Schonwald, 2004).

2.4.3.1.2 Metal fume fever

Metal fume fever (MFF) or better known as *inhalation fever* is an acute self-limiting illness resulting from inhalation of various agents including organic dusts, flax, polymers and metal oxides. These exposures cause rapid onset of this illness which may result in fever, chills, fatigue, myalgias and dyspnea and elevated white blood cell count on a peripheral smear. MFF was found as the effect of zinc oxide fumes on smelter workers but was later also associated with oxides of antimony,

aluminium, beryllium, cadmium, copper, magnesium, manganese, tin and vanadium (Keyes, 2004; Phillips and Delgado, 2004). These exposures usually occur in the context of smelting, cutting or welding, mainly in enclosed or poorly ventilated spaces (Phillips and Delgado, 2004). MFF has various synonyms such as Monday fever, brass chills, zinc ague as well as welder's ague. Previous estimations determined that as many as one in five welders have experienced MFF by the age of 30 years (Keyes, 2004). It is known that this fever is caused by the release of various inflammatory mediators and cytokines in response to stimulation by inhaled metal oxides, such as Mn. No previous sensitisation is necessary for metal fume fever to occur (Phillips and Delgado, 2004).

2.4.3.1.3 Manganese madness

Another illness known as *manganese madness* may also occur in patients who are overexposed to Mn. These patients are aware of their irregular actions but appear incapable of controlling their behaviour. Symptoms such as nervousness, irritability, aggression and destructiveness, with bizarre compulsive acts such as uncontrollable spasmodic laughter or crying, impulses to sing or dance, or aimless running, may occur (Schonwald, 2004; Winder, 2004; Antonini *et al.*, 2006b; Bowler *et al.*, 2006).

2.4.3.2 Neuroendocrine toxicity

A main neurotransmitter, known as dopamine, plays an important role in the modulation of the cognitive function, working memory, attention of the prefrontal cortex and the hippocampus. Dopamine is responsible for the regulation of thyroid stimulating hormone (TSH) secretion as well as TSH subunit secretion where dopamine and dopaminergic receptors are also involved in neurodevelopment (Soldin and Aschner, 2007). Dopamine and thyroid releasing hormone (TRH) are also hormones which influence prolactin (PRL). Dopamine causes suppression of the hypothalamic and pituitary hormone but decreases with Mn exposure, resulting in suppression of PRL and TRH (Fitsanakis *et al.*, 2006). A study conducted by Kim *et al.* (2007) concluded that there was a rise in PRL, LH and FSH levels in workers exposed to Mn. The rise was said to be due to an increased level of TRH and a decrease of dopamine. Mn toxicity therefore occurs due to a disruption of homeostasis between dopaminergic tonic control and PRL regulation. There is

uncertainty as to whether Mn exposed workers will experience clinical impairment of the endocrine system but an over exposure of Mn may lead to thyroid homeostasis disturbance due to the loss of dopaminergic control of TSH regulation of thyroid hormones, causing adverse neurodevelopmental effects (Kim *et al.*, 2007; Soldin and Aschner, 2007).

2.4.3.3 Pulmonary toxicity

Upper and lower respiratory tract infections shows a decrease regarding the incidence, severity and duration in welders in relation to the general population (Antonini *et al.*, 2003; Antonini *et al.*, 2011). An inflammatory response in the lung may occur due to inhalation of Mn -containing dust in certain occupational settings (Liu *et al.*, 2008). Elder *et al.* (2006) conducted a study on the exposure of Mn oxide ultrafine particles and found a decrease in lung lavage fluid β -glucuronidase activity after 12 days. Antonini *et al.* (2006b) stated that the majority of full-time welders experience some type of respiratory disorder during their time of employment. Lung irritation or injury may result from inhalation of submicron aerosols, causing pulmonary effects such as metal fume fever, cough, bronchitis, asthma, lung function decrements, increased susceptibility to infection, pneumonitis, pneumonia and a possible increase in the incidence of lung cancer (Antonini *et al.*, 2003; Antonini *et al.*, 2006b; Liu *et al.*, 2008).

The occurrence of bronchitis as respiratory impairment already appeared in surveys done on full-time welders with chronic exposures late in the 1900's (Sferlazza and Beckett, 1991). Studies embarked upon in the past have also stated that inhalation of welding fumes may cause inflammatory lung diseases such as asthma (Simonsson *et al.*, 1995; Beach *et al.*, 1996; Speizer, 2000; Pascal and Tessier, 2004). Fume exposure during occupational welding will result in an increase in metal concentration in biological fluids, causing an increase in systemic inflammation (Du Plessis *et al.*, 2010). The exposure of welders to high concentrations of welding fumes in confined, poorly ventilated spaces also indicated large decrements in lung function in relation to welders working in well-ventilated areas (Antonini *et al.*, 2003). The risk of developing lung cancer is narrowed to stainless steel welding, while mild steel welding, which accounts for 80 – 90 % of all welding in industries, carries a low risk of lung cancer (Antonini *et al.*, 2003).

Ultrafine-sized Mn particles, especially nanoparticles in welding fumes may be more pneumotoxic, and have elevated deposition in the lungs in comparison with larger-sized particles compared on a mass basis although it is said that the variation in the number of ultrafine welding particles may not always be the primary reason for lung toxicity. Differences in pulmonary response may be due to alterations in the levels of different metal oxidation species instead of the quantity of metals present in the fume. These changes may cause pulmonary toxicity (Oberdörster *et al.*, 1992; Brown *et al.*, 2001; Brown *et al.*, 2002; Oberdörster *et al.*, 2005; Antonini *et al.*, 2011). Animal studies also confirmed that different metal compositions produce different pulmonary toxicities. The presence of other toxic metals such as chromium and nickel in stainless steel welding fumes cause a greater risk to respiratory health in comparison with mild steel welding fume containing Fe and Mn (Antonini *et al.*, 2003).

2.4.3.4 Cardiovascular toxicity

Mn is responsible for dilating blood vessels and induces hypotension (Liu *et al.*, 2008). Liu *et al.* (2008) also stated that cardiovascular function in animals and humans may be altered by Mn exposure and may be seen via abnormal electrocardiograms and the inhibition of myocardial contraction.

2.4.3.5 Hepatobiliary toxicity

A study conducted by Antonini *et al.* (2009) discovered a significant increase for liver Fe and kidney Mn in the animal group exposed to welding fumes, which was compared to control animals exposed to filtered air. The lack of an increase of Mn in the liver supported the fact that biliary excretion of Mn was enhanced after inhalation. Combined with bilirubin, Mn produces intrahepatic cholestasis by acting on the synthesis and degradation of cholesterol and inhibition of the membrane transport pump, Mrp2 (Liu *et al.*, 2008). Dorman *et al.* (2006) stated that Mn toxicity may occur easier in individuals with compromised hepatic function. Whenever patients experience hepatobiliary insufficiency due to cholestatic liver disease, biliary atresia or hepatic encephalopathy Mn body burden will increase due to a reduction of Mn excretion. Liver diseases such as cirrhosis decrease hepatobiliary Mn excretion

when inhalation of Mn fumes occurs, causing an enhanced delivery of Mn to the brain (Dorman *et al.*, 2006; Liu *et al.*, 2008).

2.4.3.6 Reproductive toxicity

Gerber *et al.* (2002) stated that the fertility in mammals is affected by large quantities of Mn exposure causing embryo and foetus toxicity. Therefore pregnant woman should not be exposed to Mn at the workplace. Testicular dysfunction due to long term accumulation of Mn was also indicated in a study conducted by Ellingsen *et al.* (2007) although testicular pathology combined with impairment is unknown in PD patients. Taube (2012) stated that overexposure to inhaled Mn is a higher risk of developing infertility in the case of male workers.

In accordance with Aschner *et al.* (2007) the conclusion can therefore be drawn that high dose exposure to Mn will cause an increase in tissue Mn levels which may result in adverse neurological, respiratory and reproductive effects.

2.4.3.7 Oxidative Stress

Oxidative stress has been a concern in many human diseases including cancer, immunosuppression and neurodegenerative diseases (Du Plessis *et al.*, 2010). Oxidative stress is known to cause cell injury by damaging carbohydrates, lipids, proteins, nucleic acids and DNA. This damage may eventually cause cell death. The damage will also cause depletion of glutathione (GSH) which may result in a decrease of antioxidant ability (Reaney and Smith, 2005; Du Plessis *et al.*, 2010). Superoxide dismutase (SOD) or Malondialdehyde (MDA) or even both, is seen as helpful oxidative stress biomarkers in the systemic circulation of welders being exposed to long term, low-levels welding fumes (Li *et al.*, 2004). The measurement of reactive oxygen species (ROS) levels, damage caused by ROS and antioxidant status may also be other approaches to determine a sound overview of the oxidative status (Reaney and Smith, 2005; Du Plessis *et al.*, 2010).

According to researchers, the Mn ion (Mn^{2+}) enhance the autoxidation or turnover of a variety of intracellular catecholamines, leading to the production of increased free

radicals, ROS, and other cytotoxic metabolites as well as causing depletion of cellular antioxidants (Garner and Nachtman, 1989; Verity, 1999).

A study (Limbach *et al.*, 2007) showed that generation of ROS in human lung cancer cells (A549) were caused by Mn (II, III) oxide nanoparticles. Studies show that Mn overexposure cause an enhancement of neuronal oxidative stress and neuroinflammatory biomarkers due to the inhibition of enzymes involved in cholinergic transmission, such as acetyl cholinesterase (AChE) (Liapi *et al.*, 2008; Santos *et al.*, 2012). This occurrence of oxidative stress due to high levels of Mn exposed welding fumes will compromise cell survival and lead to apoptosis (Santos *et al.*, 2012). A study conducted by Frick *et al.* (2011) found that intracellular oxidative stress and alveolar epithelial cell apoptosis occur due to the uptake of Mn₃O₄ nanoparticles. Donaldson *et al.* 1996 as well as Donaldson *et al.* 2009 proposed that whenever one is exposed to nanoparticles, it can be seen as the response to oxidative stress which would lead to anti-oxidant defence, proinflammatory signalling and induction of apoptosis.

2.4.3.8 Carcinogenicity

According to the International Agency for Research on Cancer (IARC, 1990), there is limited evidence in humans for the carcinogenicity of welding fumes and gases as well as inadequate evidence in experimental animals. The overall evaluation therefore stated that welding fumes are '*possibly carcinogenic*' to humans (Group 2B). This can be ascribed to the fact that known human carcinogens such as hexavalent chromium (Cr) and nickel (Ni) form part of the fume derived during stainless steel welding. Information regarding carcinogenicity in Mn exposed workers is very little, but results available do not indicate that inorganic Mn is carcinogenic, even though it causes mutations (Schonwald, 2004). Liu *et al.* (2008) states that inorganic Mn is not carcinogenic in humans or rodents and tests negative in the Ames test. Although it is classified as none carcinogenic, Gerber *et al.* (2002) stated that Mn exposure decreases the fidelity of DNA replication in human peripheral lymphocytes by modifying the activity of DNA polymerase. DNA damage and chromosome aberration was found in mammalian cells exposed to Mn. Mn²⁺, however does not seem to obstruct the repair of chemically induced DNA damage. In conclusion, recent studies claim that many occupational respiratory diseases, of

which lung cancer is part, are triggered due to the inhalation of welding fumes (Frick *et al.*, 2011; Sriram *et al.*, 2012).

2.5 OCCUPATIONAL EXPOSURE: MONITORING OF EXPOSURE AND TREATMENT FOR MANGANESE TOXICITY

2.5.1 Personal monitoring

An important notion in occupational exposure evaluation relates to personal sampling for chemical agents in the 'breathing zone' (Lidén and Surakka, 2009). Many definitions exist referring to the breathing zone. For example, the international standard on the sampling of airborne particles during welding, defines the breathing zone of the welder as being 'behind the welder's face shield when worn' (ISO, 2001). Occupational Safety and Health Administration (OSHA) defines it as being 'within a ten inch (25.4 cm) radius of the worker's nose and mouth' (OSHA, 2012a). According to Kareis (2009) a breathing zone is the area from where the employee receives a draft of air and has been defined as being as close as possible to the nose and mouth and a hemisphere forward of the shoulders within a 15.2 cm to 22.9 cm (6 to 9 inch) radius.

A variety of studies found that the variation between the concentrations calculated close to the mouth/nose and on the lapel or chest could be anything from irrelevant to two to four times larger when the worker is in near-area of the source. Other studies claimed that samples taken inside the welder's face shield and on the collar near the lower edge of the face shield had no statistically significant difference (Cohen *et al.*, 1982; Liu *et al.*, 1995; Vinson *et al.*, 2007). When a modern face shield is worn with the visor in the down position, the general definition is not appropriate due to the fact that inhaled air enters from the side of the welder's head. Movement of workers with dust on their clothes may cause the concentration measured on the lapel to be higher than the concentration at the mouth/nose (Lidén and Surakka, 2009). Therefore measuring inside the face shield or in front of the lapel/chest is within the range of the technical definitions of the breathing zone.

2.5.2 Biological monitoring

Biological monitoring consists of measuring toxicants and their metabolites or molecular signatures of their effects in specimens from humans or animals. This may be done by collecting urine, blood, faeces, exhaled breath, hair, finger- or toenails, bronchial lavage, breast milk or adipose tissue (Liu *et al.*, 2008). The internal dose of biomonitoring offer advantages over monitoring air in the workshop. Firstly, also seen as the greatest advantage, is that the fact that biological measurements are more directly related to the adverse health effects as it reflects the amount of toxicant absorbed. Secondly, biological monitoring represents uptake by all the exposure routes. When there are different routes of exposure, airborne monitoring concentrations underestimate true exposure. Thirdly, due to the fact that it can evaluate the overall exposure, biological monitoring may also be used to determine the efficiency of personal protective equipment such as respirators, gloves or barrier creams. Fourthly and lastly is the fact that biological monitoring also represents non-occupational exposure such as hobbies, residential exposure, dietary habits, smoking and second jobs. Biological monitoring is thus able to determine one internal load, obtained via the total external exposure (environmental and occupational). When the relationships between external exposure, internal dose and adverse effects are established it increases the importance of biological monitoring (Liu *et al.*, 2008).

A recent study done by Sriram *et al.* (2012) concluded that nail Mn has the potential to be a responsive and dependable biomarker for welding fume-related Mn exposure and neurotoxicity. It is said that nail clippings are also an attractive substitute for biomonitoring welding fume exposures in occupational settings due to the fact that it can be collected, stored and transported with relative ease (Sriram *et al.*, 2012).

Nails are a modified form of human tissue consisting of hard keratin which is rich in sulphur and glycine-tyrosine matrix proteins. This sulphur-rich keratin which is present in hair and nail has a high affinity for metal cations such as Mn, making the nail a reliable matrix for evaluation of metal toxicity (Sriram *et al.*, 2012). The nail plate is formed by layers of keratinised cells produced by the nail matrix which is a highly proliferative epidermal tissue. The cytoplasmic keratin mass is partially crystalline and partially amorphous. The keratinisation occurs both on the dorsal and

ventral side of the nail plate. The nail plate covers the nail bed which is a non-cornified tissue. At the edge the nail bed cells are carried distally by the nail plate during the growth towards the free margin. Nails grow in two different directions, length and thickness. The proliferation of the matrix involves the distal growth of the nail while the thickness of the nail depends on the formation of ventral layers by the nail bed during growth from the lunula to the free margin. The continuous production of ventral nail provides a large route of rapid access which operates along the whole length of the nail (Palmeri *et al.*, 2000).

Several studies showed the occurrence of drugs in distal nail clippings earlier than would be accepted if the drug was incorporated only via the nail matrix. This is due to the incorporation via the nail bed (Fig. 1). The appearance of labelled cells in the nail bed at one or two week intervals provide the evidence that cell migration occurs from the nail matrix into the nail bed (Norton, 1971; Finlay *et al.*, 1990; Matthieu *et al.*, 1991; Willemsen *et al.*, 1992; Schatz *et al.*, 1995; Faergemann and Laufen, 1996; Palmeri *et al.*, 2000).

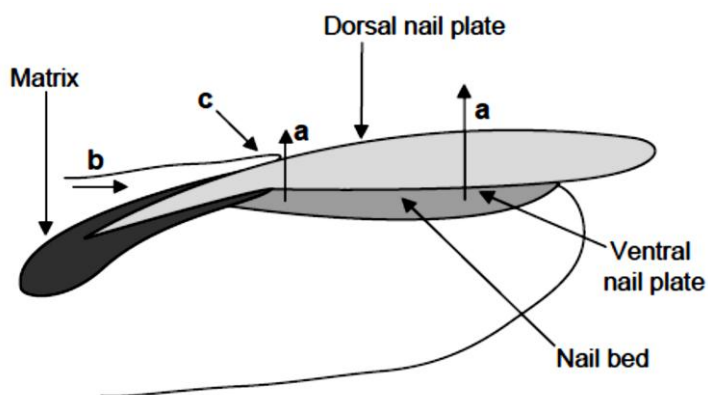


Figure 1: Mechanisms of drug incorporation into nails. **a** = via nail bed (thickening); **b** = via matrix (linear growth); **c** = environmental contamination (Palmeri *et al.*, 2000).

2.5.3 Treatment for manganese toxicity

When a welder is acutely exposed to Mn, decontamination includes removing the welder from the contaminated area as well as the removal and isolation of contaminated clothing. It is important that eyes are immediately flushed with water after ocular exposure. The skin also needs to be washed immediately with soap or

mild detergent and water. When the welder is in respiratory distress, ventilation support needs to be provided and oxygen should be administered. Bronchospastic symptoms following acute inhalation may theoretically react to inhaled bronchodilators and steroid therapy (Schonwald, 2004).

Symptomatic therapy is limited, has highly divergent results depending on the area of the brain having been damaged (Bowler *et al.*, 2006). Neurological signs of manganism may be alleviated by chelation therapy with agents such as calcium disodium ethylenediaminetetraacetic acid and calcium trisodium pentetate, but the response is usually not all that successful. These agents may either reduce the body burden or decrease the serum levels and increase urine excretion of Mn. Another method is to reverse some of the neuromuscular signs of manganism by using antiparkinsonian drugs such as Levodopa[®]. Although these drugs may reverse signs of manganism they are ineffective in improving the symptoms of manganism (Schonwald, 2004).

A study of seven Chinese welders with manganism was undertaken and it was discovered that ethylene diamine tetra acetic acid (EDTA) treatment increased Mn excretion in urine and decreased Mn concentrations in blood. Although clinical symptoms are not significantly alleviated, EDTA chelating therapy would still be helpful in reducing blood Mn levels in patients poisoned with Mn (Crossgrove and Zheng, 2004). EDTA's structure consists of four carboxyl groups. Although these groups are essential to chelating, it also renders the molecule poorly lipophilic and prevents it from crossing the blood-brain barrier. EDTA primarily chelates the extracellular Mn ions. An antibacterial drug, sodium para-aminosalicylic acid (PAS) has emerged as a treating drug for severe manganism. This Food and Drug Administration (FDA) – approved drug was initially used for tuberculosis (TB) treatment but provides an ideal chelating moiety for metals (Aschner *et al.*, 2007).

Without treatment, symptom severity will increase and the recovery ability would decrease. A few therapeutic treatments have been researched and documented as possibilities to induce Mn intoxication. The treatment with L-dopa is applied as it tends to control or improve the overwhelming symptoms associated with extrapyramidal damage. A neurologist also uses L-dopa as a diagnostic tool to

distinguish between manganism and PD, although L-dopa has partial benefits in improving clinical symptoms among manganism patients (Aschner *et al.*, 2007).

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CHAPTER 3: ARTICLE

The article in this chapter will be presented according to the requirements of the journal *Annals of Occupational Hygiene*.

3.1 Instruction to authors (Annals of Occupational Hygiene)

Originality: Material should be original when submitted and not under consideration elsewhere. If the findings have been published elsewhere in part, or if the submission is part of a closely-related series, this must be clearly stated in the letter accompanying the manuscript, and the submitted manuscript must be accompanied by a copy of the other publications (or by a copy of the other manuscripts if they are still under consideration).

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Title, abstract and keywords: These are important because most readers find papers by internet search of subjects, not by browsing the journal. Recognisable, searchable terms and keywords must be included to enable readers to more effectively find your paper. The title should clearly summarise the subject of the

paper. The abstract should contain the top five words and phrases that an internet searcher who is interested in your paper might use.

Authorship: Persons should only be named as authors if they have made significant identifiable intellectual contributions to the work; other contributions may be recognised by acknowledgement at the end of the submission.

Structure of paper: Papers should generally conform to the pattern: Introduction, Methods, Results, Discussion, and Conclusions, unless these are clearly inappropriate. A paper must be prefaced by an abstract of the argument and findings, which may also be arranged under the same headings.

Design and analysis: The quality of the data and analysis must always be good enough to justify the inferences and conclusions drawn. Particular attention should be given to design of sampling surveys, which should be planned using modern statistical principles, and to the treatment of results below the limit of detection.

Units and symbols: SI units must be used, though their equivalent in other systems may be given as well.

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Examples:

Simpson AT, Groves JA, Unwin J, Piney M. (2000) Mineral oil metal working fluids (MWFs)—Development of practical criteria for mist sampling. *Ann Occup Hyg*; 44: 165-72.

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Swift DL, Cheng Y-S, Su Y-F, Yeh H-C. (1994) Ultrafine aerosol deposition in the human nasal and oral passages. In Dodgson J, McCallum RI, editors. *Inhaled particles VII*. Oxford: Elsevier Science. p. 77-81. ISBN 0 08 040841 9 H.

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Morse SS. (1995) Factors in the emergence of infectious diseases. *Emerg Infect Dis* [serial online] 1995 Jan-Mar;1(1). Available from: URL: <http://www.cdc.gov/incidod/EID/eid.htm> (accessed 25 Oct 2010)

Ethics: If requested, authors must produce original data for inspection by the editor. Possible fraud may be referred to the authors' institutions. Studies carried out on human subjects, other than measurements in the course of their normal work activities, must have been approved by a competent ethics committee using the standards of the Helsinki Declaration of the World Medical Association. The ethics committee who gave approval must be named in the paper.

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3.2 Article

EXPOSURE OF WELDERS TO MANGANESE IN WELDING FUMES

M. FERREIRA, P.J. LAUBSCHER AND J.L. DU PLESSIS

Subject Group Physiology, Faculty of Health Sciences, North-West University,
Potchefstroom Campus, Private Bag X6001, Potchefstroom 2520, South Africa.

Corresponding author

PJ Laubscher

Tel: +27-18 299 2441

E-mail: petrus.laubscher@nwu.ac.za

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ABSTRACT

The general aim of this study was to determine the personal respiratory exposure and biological monitoring of manganese (Mn) present in welding fumes as well as its neurological influence on welders. A gravimetric method was used to determine the respiratory exposure of welders. A cassette containing a 0.8- μm cellulose ester membrane filter, attached to the side of the welding helmet provided, was connected via a stainless steel fitting to the inside (respiratory zone) of the helmet. Chemical analysis (metal content) of the welding fumes was conducted according to the NIOSH 7300 method using Inductively Coupled Argon Plasma, Atomic Emission Spectroscopy (ICP-AES). Nail clippings were collected at the beginning and end of the study in order to determine the Mn level in the nails in both welders as well as paired controls. The nails were deposited into small, plastic vials and also analysed according to the above mentioned method. A Perdue pegboard and mirror drawing test was also conducted so as to determine the influence of Mn exposure on finger dexterity and hand-eye coordination of welders. Mn exposure in the welding fumes did not exceed the occupational exposure limit – recommended limit (OEL-RL) (1 mg/m^3) of the Regulations for Hazardous Chemical Substances (RHCS), although two of these exposures exceeded the action level (0.5 mg/m^3). No statistical significant correlations were found between the Mn respiratory exposure and the Mn found in the nails of the welders. Mn in the nails of exposed welders was statistical significantly higher ($p = 0.003$) than that of controls. The only statistical significant differences found in the motor function tests between the controls and welders was the test which was done by using their non-dominant hand at the beginning of the study ($p = 0.016$) and when the non-dominant hand values were pooled ($p = 0.012$). The usage of both hands simultaneously showed results which leaned toward a statistical significant decrease of the welders compared to the control subjects ($p = 0.090$). In all these cases the controls inserted more pins than the welders. Only one moderately positive correlation ($r = 0.612$; $p = 0.02$) was found between Mn in the welding fumes and the number of errors made in the mirror drawing coordination test done by the welders. The Mn in the nails of the control group was significantly lower than the Mn in the nails of the welders. This indicates that Mn respiratory exposure may influence Mn body burden although no correlation between Mn in welding fumes and Mn in nails were found. Nail Mn may serve as a biomarker to determine Mn

body burden. Only the use of the non-dominant hand of the control subjects compared to the welders showed a significant decrease in finger dexterity of the welders. The moderately positive association between the Mn in the welding fumes and the number of errors made in the mirror drawing coordination test done by the welders indicates that with an increase in Mn in welding fumes, a decrease in hand-eye coordination will occur. It can be concluded that a welder's finger dexterity and hand-eye coordination may be influenced by the exposure to Mn in the welding fumes.

INTRODUCTION

Occupational exposure to manganese (Mn) normally occurs in mines, smelters, boiler shops and dry-cell battery factories (Aschner *et al.*, 2007; Liu *et al.*, 2008). Welding fumes released in boiler shops, for instance, consist of the hazardous metal oxide, Mn (Antonini *et al.*, 2006a). Mn is not only an essential element for normal development and body function in mammals, but also an necessary product in the welding of steel (Harris, 2002; Schonwald, 2004; Jenkins and Eagar, 2005). Mn increases the metallurgical properties, hardness and strength of steel and assists in forming a stable weld by acting as a deoxidizing agent (Harris, 2002). The different oxidation states in which Mn occurs, the most commonly found ion being Mn^{2+} , causes it to have different soluble properties (Antonini *et al.*, 2006b). The oxidation of divalent Mn may also lead to the development of the more reactive and toxic trivalent Mn (Schonwald, 2004; Liu *et al.*, 2008).

Mn can easily enter the brain through mechanisms of Mn transport across the blood-brain barrier (BBB), causing neurotoxicity (Aschner *et al.*, 2007). Whenever a worker is exposed to high concentrations of Mn, this causes the brain Mn to increase. Said increase normally takes place in the substantia nigra, basal ganglia, caudate putamen, globus pallidus, and subthalamic nuclei. These are all areas where high concentration levels of non-heme iron occur. Once Mn levels elevate in the brain, a critical condition namely Manganism develops (Beuter *et al.*, 2004; Li *et al.*, 2004; Santamaria and Sulsky, 2010). Manganism is seen as a CNS abnormality with neuropsychiatric disturbances; it is said to be very similar to Parkinson's disease (PD) due to the fact that widespread rigidity and tremors are mutual symptoms (Ellingsen *et al.*, 2008). *Metal fume fever* (Keyes, 2004; Phillips and Delgado, 2004) and *manganese madness*, (Schonwald, 2004; Winder, 2004) are other illnesses which may occur due to occupational over exposure to Mn. According to Aschner *et al.* (2007), a variety of psychiatric and motor disturbances may also arise from Mn toxicity. Beuter *et al.* (2004) concluded that Mn exposure is responsible for the increase in the regularity of tremors. Bowler *et al.* (2007) and Haynes *et al.* (2012) stated that neuropsychological, motor functions and coordination impairment form part of the neurotoxicological effects of Mn. Once there is an abnormally high concentration of Mn in the brain, especially in the basal ganglia, neurological

disorders may occur; yet even early Mn neurotoxicity has been observed to cause mild and severe impaired motor functions (Takeda, 2003; Liu *et al.*, 2008; Chang *et al.*, 2009). According to Wastensson *et al.* (2012), long term exposure to Mn in welding fumes cause adverse effects on the motor function of welders.

The duration of career welding is a variable which needs to be considered when occupational Mn toxicity is assessed. An increase in the duration of career welding has been associated with the development of neurological dysfunction (Aschner *et al.*, 2007). Erikson *et al.* (2004) concluded that age is another variable which needs to be taken into account when assessing occupational Mn toxicity. Older employees in the workplace have a higher risk of developing Mn toxicity, causing the aged nervous system to be influenced negatively (Chu *et al.*, 2002; Dorman *et al.*, 2006). According to Bowler *et al.* (2006), manganism is also being observed in younger workers. Li *et al.* (2004) observed that younger, inexperienced welders (≤ 30 years) have a higher serum Mn level (0.39 $\mu\text{g/dL}$) than older, more experienced welders (31 – 40 years; average 0.26 $\mu\text{g/dL}$). This may cause the younger welders to suffer from adverse health effects at an earlier age. A faster breathing rate, more dynamic cardiac functions, longer hours or unsafe working conditions due to inexperience, differences in toxicokinetics as well as variations in biochemical parameters are all factors which may cause the younger welders to have a higher serum Mn level in comparison to the older welders (Li *et al.*, 2004). Chu *et al.* (2002) and Dorman *et al.* (2006) are opposed to Li *et al.* (2004) and the implementation of different biological matrices to conclude whether or not younger welders are more vulnerable when exposed to Mn in welding fumes compared to older welders.

The occupational exposure limits (OELs) for Mn as a fume varies internationally. The South African occupational exposure limit – recommended limit (OEL-RL) for Mn is consistent with the National Institute for Occupational Safety and Health (NIOSH, USA), recommended exposure limit (REL) of 1 mg/m^3 as an eight hour time weighted average (TWA), and 3 mg/m^3 as a short term exposure limit (STEL) (RHCS, 1995; NIOSH, 2010). The Occupational Safety and Health Administration (OSHA) only have a permissible exposure limit (PEL) of 5 mg/m^3 (ceiling limit) while the American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) of 0.2 mg/m^3 which is consistent with the

level limit value (LLV) for total Mn dust, established by the Swedish Work Environment Authority (SWEA). The SWEA also established a LLV for respirable Mn dust (0.1 mg/m^3) (SWEA, 2005; ACGIH, 2012; OSHA, 2012).

The most widely used matrices for the determination of Mn in welding fumes are blood and urine (Winder, 2004); none of these matrices have however proven reliable (Aschner *et al.*, 2007). Blood Mn is not an indicator of total Mn body burden due to intracellular distribution, and the relative short half-life Mn has in the blood compartment. Urine is less of a Mn toxicity indicator due to the fact that more than 95% of Mn is excreted via bile to faeces (Gil *et al.*, 2011). A recent study performed on animals suggested that the use of nail clippings could be a reliable indicator of Mn body burden (Sriram *et al.*, 2012). Nails containing keratin is said to be rich in sulphur. Nails therefore have a high affinity for metal cations such as Mn (Palmeri *et al.*, 2000; Sriram *et al.*, 2012). Whether or not Mn will be detected in nails a week or two after Mn exposure is proven by the fact that drugs can be detected in nail clippings as early as only one or two weeks after administration (Matthieu *et al.*, 1991; Schatz *et al.*, 1995; Faergemann and Laufen, 1996). The incorporation occurs via the nail matrix into the nail bed. After the incorporation it diffuses through the nail plate moving from the nail bed to the most distal segment of the nail where the clipping is sampled (Palmeri *et al.*, 2000).

Measuring fine motor control and coordination can be carried out by using a pegboard test to determine the motor dexterity and a mirror drawing test to determine hand-eye coordination (Gallus and Mathiowetz, 2003; Midorikawa *et al.*, 2008; Tiffin, 2008). Nail clippings as matrix and the Perdue pegboard and mirror drawing tests as dexterity and coordination indicators will serve as a reliable selection to determine the exposure of welders to Mn in welding fumes, as well as to substantiate previous literature regarding Mn toxicity. The general aim of this study was to determine the personal respiratory exposure and biological monitoring of Mn present in welding fumes as well as its neurological influence on welders.

MATERIALS AND METHODS

Study population

The subjects ($n = 14$) were welders recruited from three different engineering firms where welding occurred. The control population ($n = 14$) was gathered from non-welding working environments (grocery stores and security gates) and paired with the welders for age, ethnicity and smoking habits. The controls were never employed as welders. All participants were male.

Personal respiratory sampling

The welders were monitored in the workshops for an 8-hour shift in order to make the data comparable with the TWA-OEL of Mn exposure. A cassette containing a 0.8- μm cellulose ester membrane filter was attached to the outside of the welding helmet provided drawing air via a stainless steel fitting from the inside of the helmet (respiratory zone). It caused no discomfort nor interfered with the welding task at hand. A Gilian (Gilair-3) air sampling pump with a flow rate of 2 L/min was used. The welders refrained from removing their helmets between welding tasks as well as during tea and lunch breaks. Chemical analysis (metal content) of the welding fumes was done according to the NIOSH 7300 method, using Inductively Coupled Argon Plasma, Atomic Emission Spectroscopy (ICP-AES) (NIOSH, 2003) by an accredited laboratory.

Collection and analysis of nail clippings

Biological monitoring was done by collecting nail clippings from the welders before and at the end of the study (with an interval of 3 weeks) in order to determine the Mn content in the nails. Nail clippings were also collected from the control subjects. The nail clippings from the control group were used to provide an indication of the background Mn concentration in the body, as Mn forms part of our daily diet. During the walkthrough survey the full extent of this study was communicated to the participants (both the welders and their controls) and a request was made to not clip their nails 3 weeks prior to the study.

The nails present at the tip of each finger of the participants were gently trimmed with a stainless steel surgical nail clipper. The nail clipper was rinsed with distilled water and dried between the clippings of each participant. The nails were deposited into small, plastic vials and analysed according to the NIOSH 7300 method. The nails were weighed before and after analysis so as to determine the Mn-concentration (mass Mn/mass nail clipping). The nail clippings were then ashed with a concentrated mixture of nitric acid / perchloric acid (4:1) at 120°C using a hotplate. The samples were lastly transferred to a volumetric flask and diluted to 10 ml prior to ICP-AES analysis (NIOSH, 2003).

Motor function tests

The Purdue pegboard (model 32020, Lafayette Instrument Company, Europe) was utilized to measure the upper extremity fine motor dexterity of welders exposed to Mn in welding fumes. Both the welders and the paired control group were tested. The participants were seated at a table with the Purdue pegboard stationed in front of them. The examiner explained the purpose and the procedure of the test. The procedure involved inserting pins into holes on the board, first using the dominant hand, followed by the non-dominant hand and finally using both hands simultaneously. The examiner timed them for 30 seconds using a stopwatch. The number of pins inserted successfully into the holes during an 30 second period were counted and added to form a mean value (Gallus and Mathiowetz, 2003; Tiffin, 2008).

The mirror drawing test was used to determine coordination of welders exposed to Mn in welding fumes. During the mirror drawing test participants were asked to use a pencil to trace a shape while looking at it through a mirror apparatus. Prior commencement of the test, the examiner placed the tip of the pencil at the starting position and asked the test subjects to trace the shape as fast as possible (Midorikawa *et al.*, 2008). While completing the drawing, the active hand of the participant was not directly visible. The time used to complete the drawing was notated including the number of errors determined by evaluating deviation from the original shape.

Ethical approval

This study was approved by the ethics committee of the North-West University; ethics number (NWU-00043-12-A1) (See Chapter 5, Appendix B). Upon agreement each subject signed an informed consent form.

Analysis

Mn concentrations below the detection limit (0.00010 mg/sample) of the analytical method were estimated using the β -substitution method (Ganser and Hewett, 2010). Descriptive statistics were illustrated with Box plot graphs. The mean value of the Box plot was illustrated with a cross. The outer lines of the box illustrated the 25% and 75% percentile with the horizontal line in the middle representing the median value. The whiskers of the box illustrated the minimum and maximum values. The significance of the differences between the nails of the welders and that of the control subjects measured at the beginning and end of the study, as well as the data obtained from the Purdue pegboard test and mirror drawing test was tested by Mann Witney t-tests. Pearson correlations between Mn in the welding fumes and in the nails were done. The Mn in the welding fumes was also correlated with both motor function tests. It was presented by correlation matrices. The statistical significance was set at $p \leq 0.05$. Any correlation coefficient value 0.5 – 0.8 provided a moderate to strong association with a large effect (Zou *et al.*, 2003; Steyn, 2012). The statistical analysis was done using *Statistica version 10.0* (StatSoft, 2002) and the graphs was drawn with *GraphPad Prism version 5.0* (GraphPad Prism, 2007).

RESULTS

Personal respiratory exposure of Mn in welding fumes

Gravimetric analysis of 14 personal exposure samples was collected at the beginning and end of the study, 3 weeks apart. The median Mn exposure at the beginning of the study (0.1695 mg/m³) was approximately 1.16 times higher than at the end of the study (0.1464 mg/m³) (Fig. 1). The analysis revealed that the airborne concentrations of Mn in the welding fumes was slightly lower (1.02 %) at the end of the study than at the beginning. No statistical significant difference was found between the above mentioned measurements.

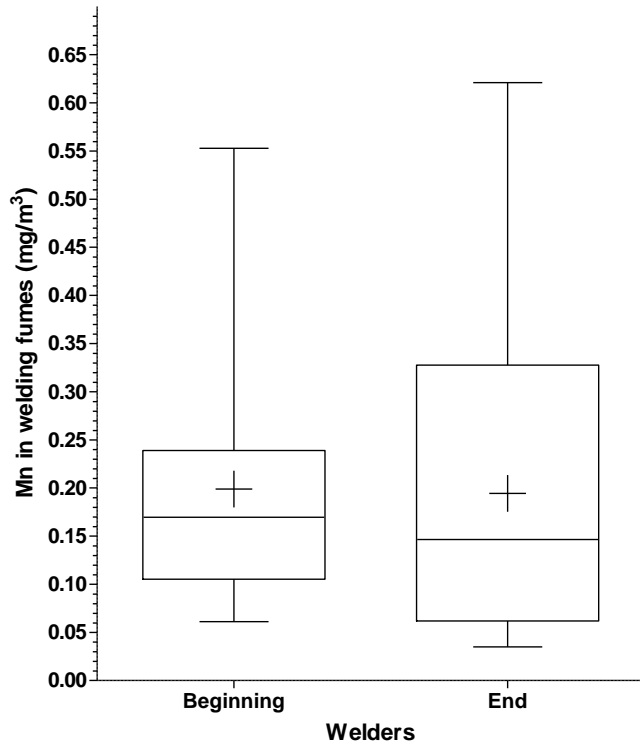


Figure 1: Box plots depicting the exposure of welders to Mn in welding fumes at the beginning and end of the study.

Figure 2 illustrates that none of the Mn in the welding fumes exceeded the RHCS OEL-RL of 1 mg/m^3 , although two of these exposures exceeded the action level (0.5 mg/m^3) (RHCS, 1995). Despite the first mentioned fact, 12 of the 28 personal respiratory exposure measurements taken exceeded the ACGIH OEL-TLV of 0.2 mg/m^3 (ACGIH, 2012).

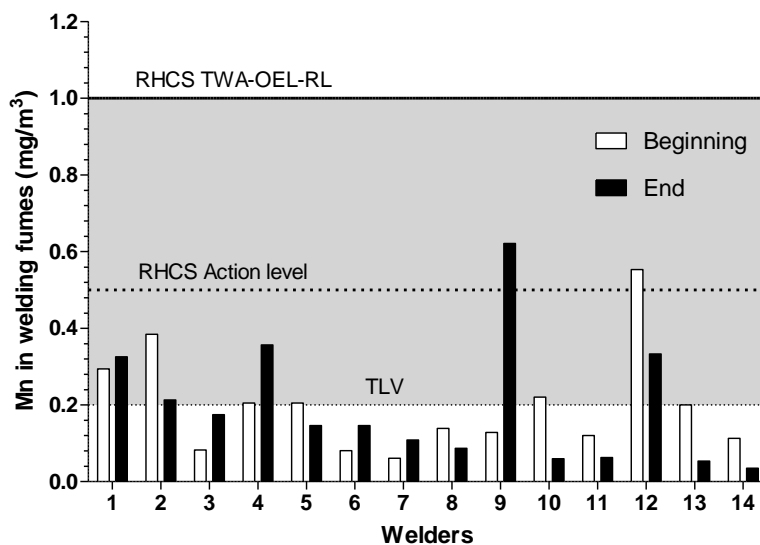


Figure 2: Personal exposure of welders to Mn in welding fumes.

Nail collections of controls and welders

The controls delivered the same median concentration at the beginning and at the end of the study (0.003 ng Mn/mg nail). The median concentrations of Mn in the nails of the welders at the beginning and end of the study were 35.424 ng Mn/mg nail and 22.690 ng Mn/mg nail respectively. The median derived from the pooled concentrations at the beginning and the end of the study of the welders was 30.540 ng Mn/mg nail. Mn in the control subjects' nails collected at the beginning of the study ranged from 0.0027 ng Mn/mg nail to 27.176 ng Mn/mg nail while those collected from the welders ranged from 15.308 ng Mn/mg nail to 217.765 ng Mn/mg nail. At the end of the study the control subjects' Mn nail ranged from 0.003 ng Mn/mg nail to 15.109 ng Mn/mg nail while those collected from the welders ranged from 0.390 ng Mn/mg nail to 125.743 ng Mn/mg nail (Fig. 3).

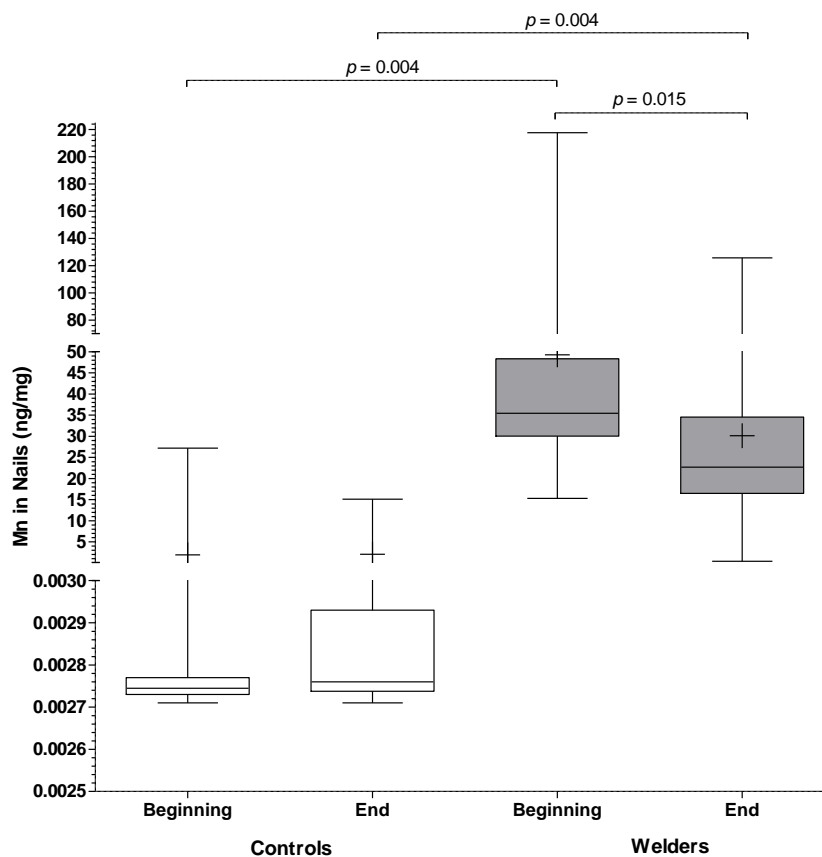


Figure 3: Box plots depicting Mn concentrations in the nails of the control subjects and welders.

The pooled Mn concentrations in the nails of the welders were statistical significantly higher ($p = 0.003$) than that of the controls.

Pearson correlations between Mn in the nails of the welders, duration of career welding and their age

A moderate correlation was found between the Mn in the nails of the welders at the beginning of the study and the duration of career welding ($r = 0.523$; $p = 0.055$). When the Mn in the nails were pooled, a weak to moderate correlation leaned towards significance ($r = 0.479$; $p = 0.083$).

Motor functions

The Perdue pegboard test was divided into 3 categories: the use of the dominant hand, the non-dominant hand and both hands simultaneously. The control subjects inserted more pins than the welders in all 3 categories at the beginning as well as the end of the study. The only statistical significant difference found between the controls and the welders were the test where they used their non-dominant hand at the beginning of the study ($p = 0.016$) and when the non-dominant hand values were pooled ($p = 0.012$). Although not significant ($p = 0.09$), the control subjects inserted more pins than the welders at the end of the study using both hands simultaneously. The control subjects showed a decrease between the beginning and end of the study using their non-dominant hand ($p = 0.082$). In the test where the welders used both hands simultaneously, a statistical significant decrease ($p = 0.049$) was found at the end of the study compared to the beginning (Fig. 4).

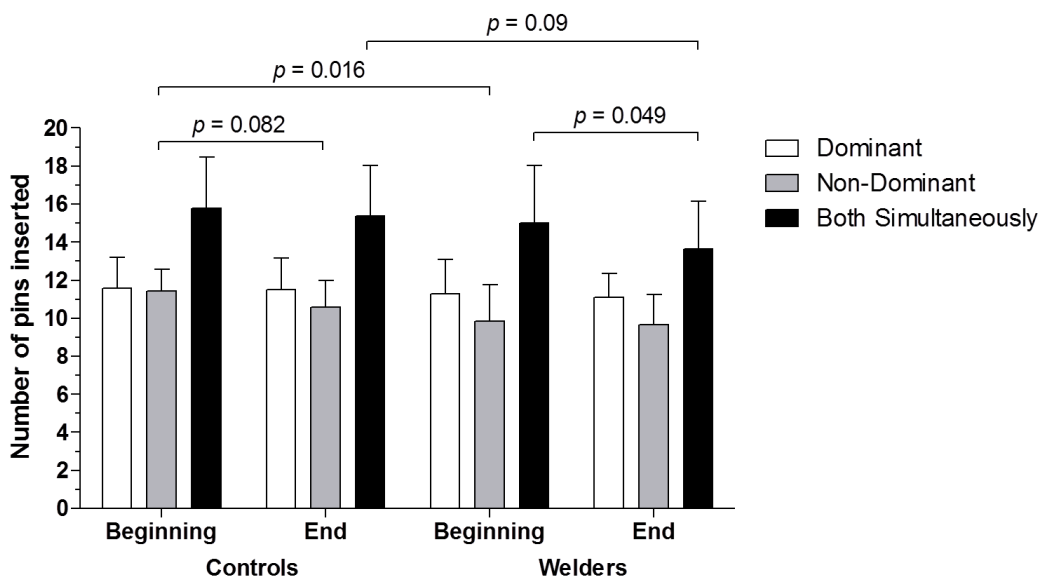


Figure 4: Perdue pegboard dexterity test. Data is depicted as mean \pm SD.

The mirror drawing test was divided into two categories i.e.: the number of errors that occurred during the drawing of the figure, and the time used to complete the drawing. The control subjects made the same number of errors at the beginning of the study as the welders, while the welders made fewer errors than the control subjects at the end of the study. At the beginning as well as at the end of the study the control subjects used less time to complete the drawing than the welders. Although differences were noticed, no statistical significant differences were found between the control subjects and welders in the mirror drawing coordination tests. There was a statistical significant decrease ($p = 0.033$) found in the time the control subjects used to complete the drawing at the end of the study compared to the beginning. The welders also showed a highly statistical significant decrease at the end of the study compared to the beginning, in the time used to complete the drawing ($p = 0.0006$) (Fig. 5).

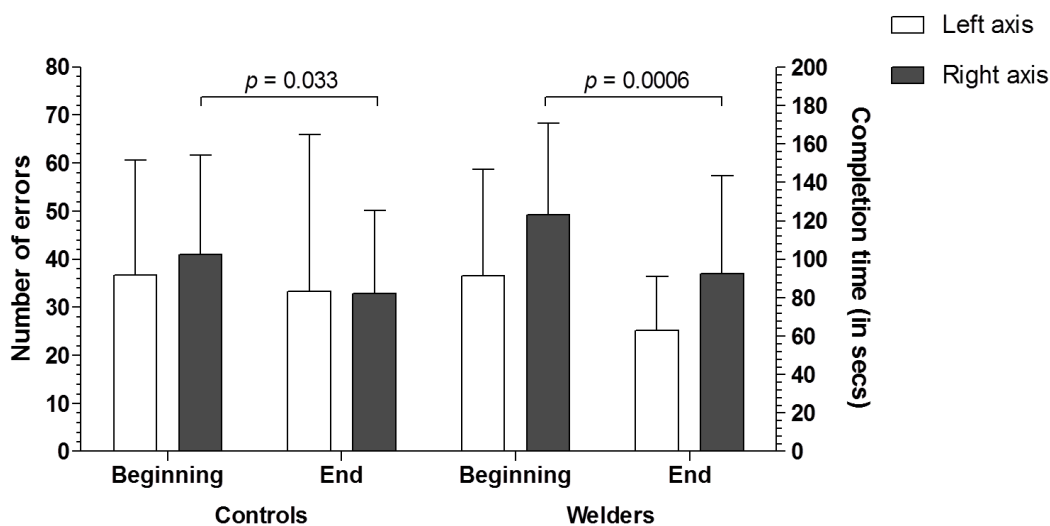


Figure 5: Mirror drawing coordination test. Data is depicted as mean \pm SD.

Pearson correlations between Mn in welding fumes, nail deposition and motor function tests.

The different correlations done between the personal respiratory exposure of welders to Mn in welding fumes, Mn in the nails of the welders and motor function tests completed by the welders are presented in Table 1.

Table 1: Pearson correlations between personal respiratory exposure, Mn in the nails and motor function tests of welders				
	<i>r</i> -values		<i>p</i> -values	
Mn in welding fumes correlated with nail Mn (Beginning)	-0.147		0.617	
Mn in welding fumes correlated with nail Mn (End)	-0.153		0.601	
	Mn in welding fumes (pooled) correlated with:		Mn in nails of welders (pooled) correlated with:	
	<i>r</i> -values	<i>p</i> -values	<i>r</i> -values	<i>p</i> -values
Mn in nails of welders (pooled)	-0.208	0.476	-	-
Perdue pegboard dexterity test (dominant)	0.343	0.231	0.091	0.756
Perdue pegboard dexterity test (non-dominant)	0.235	0.418	-0.132	0.654
Perdue pegboard dexterity test (both simultaneously)	0.104	0.724	0.083	0.779
Mirror drawing coordination test (number of errors)	0.612	0.020	-0.047	0.873
Mirror drawing coordination test (completion time of drawing)	-0.026	0.929	-0.309	0.283

According to Table 1 there was no correlation between the Mn in the welding fumes at the beginning and the end of the study. The Perdue pegboard dexterity test also showed no correlation with the Mn in the welding fumes or the Mn in the nails of the welders. The only significant correlation was between the Mn in the welding fumes (pooled) and the amount of errors which occurred during the mirror drawing coordination test done by the welders ($r = 0.612$; $p = 0.02$).

DISCUSSION

This study determined the personal respiratory exposure and biological monitoring of Mn in welding fumes of 14 welders and the influence it has on their neurological systems. Mn is not only known to be beneficial to the body, but may cause severe health effects when exposed to in welding fumes (Schonwald, 2004; Jenkins and Eagar, 2005; Liu *et al.*, 2008; Taube, 2012). Mn is considered to be toxic toward the CNS, neuroendocrine-, pulmonary-, cardiovascular-, hepatobiliary-, and reproductive system. Oxidative stress and carcinogenicity may also occur due to the Mn exposure in welding fumes (IARC, 1990; Gerber *et al.*, 2002; Antonini *et al.*, 2003; Antonini *et al.*, 2006b; Kim *et al.*, 2007; Soldin and Aschner, 2007; Liu *et al.*, 2008; Du Plessis *et al.*, 2010; Frick *et al.*, 2011).

In this study the personal respiratory exposure of welders to Mn in welding fumes were seen to be below the RHCS OEL (1 mg/m^3) (Fig. 2). A study done by Roels *et al.* (1992) observed adverse health effects at respiratory exposure levels as low as 0.15 mg/m^3 . Several more recent studies revealed that personal respiratory Mn exposure at levels as low as 0.027 mg/m^3 cause neurotoxicity (Lucchini *et al.*, 1999; Bowler *et al.*, 2007; Liu *et al.*, 2008). The ACGIH decreased its TLV to 0.2 mg/m^3 . Evidence suggested that any limit higher than that may not be protective enough for the welders (AGCIH, 2012). It was noted that none of the welders wore respiratory equipment, increasing the inhalation possibility of welding fumes.

The use of nail clippings can be a responsive and a dependable biomarker to determine welding fume-related Mn exposure and neurotoxicity (Sriram *et al.*, 2012). With caution, it can be said that this study agrees with the statement made by Sriram *et al.* (2012) which stated that nail clippings can be a dependable biomarker as the results of the nail clippings of the welders showed higher levels of Mn (19.69-fold) compared to that of the controls. It is assumed that the exposure to Mn in the welding fumes increased the Mn in the nails due to the high difference in Mn between the controls and the welders. Respiratory exposure at the beginning (median = 0.1944 mg/m^3) and at end (median = 0.1464 mg/m^3) of the study did not differ significantly. Although there was a significant decrease of Mn in the nails of the welders at the end of the study ($p = 0.015$), it was still higher than the Mn levels of the controls (Fig. 1 and 3). The higher statistical significant concentration of Mn in nails of welders in comparison with the non-exposed controls provides the indication that Mn in welding fumes may have an influence on the deposition of Mn in nails. It is important to remember that the dynamics of Mn-nail fixation are complicated and may be influenced by unknown factors. The Mn in the nails of the controls (pooled) showed a lower statistical significant concentration ($p = 0.003$) in comparison with the welders (pooled) which indicates that the background Mn in a human body, not being exposed to welding fumes, is very low. A study done by Sriram *et al.* (2012) exposed rats to gas metal arc-mild steel (GMA-MS) and manual metal arc – hard surfacing (MMA-HS) welding once a week for 28 weeks. The nail clippings of the rats showed a mean Mn concentration of $0.60 \text{ ng Mn/mg nail}$ for GMA-MS welding and $2.20 \text{ ng Mn/mg nail}$ for MMA-HS welding. Both these Mn concentrations were significantly higher than the controls due to Mn exposure in welding fumes. Strong

correlations were found between the Mn in the nails of the rats and the striatum and midbrain causing dopaminergic abnormalities (Sriram *et al.*, 2012). In this study mean Mn concentrations as high as 49.25 ng Mn/mg nail and 30.14 ng Mn/mg nail were found in the nails of the welders at the beginning and end of the study with a pooled mean Mn concentration of 79.39 ng Mn/mg nail (Fig. 3). The welders mostly performed GMA-MS welding. These Mn concentrations were also significantly higher than the controls confirming the fact that the high Mn level in the nails of the welders was due to Mn exposure in welding fumes. These high Mn concentrations indicate a definite health risk in comparison with the already strong correlations and abnormalities found between the Mn concentrations in the nails of the rats and the brain.

In this study there was a correlation between Mn in the nails of the welders (pooled) and the duration of career welding, although not that significant ($r = 0.479$; $p = 0.083$). This suggests that the long term exposure to Mn in welding fumes does not necessarily trigger CNS impairment with an increase of Mn body burden. This statement is therefore in partial contradiction with Wastensson *et al.* (2012) who concluded that long term exposure to Mn in welding fumes caused an increase in body burden resulting in adverse motor function effects. No correlation between Mn nails of the welders (pooled) and their age, suggested that the welders' age does not have an influence on Mn levels in the nails. This statement disagrees with the literature that states that Mn toxicity is influenced by age (Chu *et al.*, 2002; Erikson *et al.*, 2004; Li *et al.*, 2004; Dorman *et al.*, 2006).

Several studies of welders exposed to Mn (even in small quantities, $< 0.2 \text{ mg/m}^3$) have shown a decrease in fine motor function due to accumulation of Mn in the brain causing neurobehavioral changes (Takeda, 2003; Laohaudomchok *et al.*, 2011; Taube, 2012). The controls inserted more pins than the welders in both the beginning and at the end of the study using their dominant, non-dominant and both hands simultaneously during the Perdue pegboard dexterity test. In this study the controls showed a decrease in the Perdue pegboard test between the beginning and end of the study, using their non-dominant hands, although not statistical significant ($p = 0.082$). The welders showed a significant decrease in the Perdue pegboard dexterity test using both hands simultaneously ($p = 0.049$) between the beginning and end of the study performing. The controls showed a significant higher insertion

of pins ($p = 0.016$) in comparison with the welders, using their non-dominant hand during the Perdue pegboard dexterity test (Fig. 4). Wastensson *et al.* (2012) stated that former welders performed poor in the grooved pegboard test using their dominant hand, in comparison to their controls. There was no significant difference between the welder and controls using their non-dominant hand (Wastensson *et al.*, 2012). In this study, the use of the non-dominant hand is the only result showing a significant difference between the controls who inserted more pins than the welders both at the beginning and at the end of the study.

The controls had more errors in their mirror drawing performance than the welders at the beginning as well as at the end of the study. The control subjects, however, completed the mirror drawing coordination test in less time than the welders at the beginning as well as at the end of the study. Effects which may influence the motor function tests are the fact that welding requires optimal hand steadiness and manual dexterity causing the welder to achieve above what is suspected by literature. The welders have improved skill above the controls due to the fine motor movements made every day (Wastensson *et al.*, 2012). The control subjects ($p = 0.033$) as well as the welders ($p = 0.0006$) showed a statistical significant decrease in the time it took to complete the drawing of the mirror drawing coordination test at the end of the study compared to the beginning. This may be that both the control subjects and welders were more comfortable performing the mirror drawing test the second time. The second performance may have also lead to a better understanding of the test causing a rapid completion of the drawing. Another possibility is that the decrease in nail Mn in the welders at the end of the study (Fig. 3) may have caused an increase in the speed of their motor function. Although this study cannot prove that the nail Mn is related to the Mn in welding fumes, a decrease in nail Mn may result in a decrease in Mn toxicity.

There was a moderate positive correlation ($r = 0.612$; $p = 0.02$) observed between the Mn in the welding fumes and the amount of errors in the mirror drawing coordination test done by the welders. This indicated a decrease in coordination with an increase of Mn exposure. Sriram *et al.* (2012) concluded that Mn accumulation in nail clippings of rats due to welding fume exposure was comparable to Mn levels in the brains of the rats but no other organs. Several studies show neurological and neurobehavioral effects (mood changes, short term memory loss,

prolonged reaction time and influence in accurate hand-eye coordination) when exposed to low concentrations (ranging from as low as 0.004 mg/m³ to < 0.5 mg/m³) of Mn in welding fumes (Bowler *et al.*, 2007; Chang *et al.*, 2009; Laohaudomchok *et al.*, 2011; Taube, 2012).

The small number of subjects evaluated might have had an influence on the data obtained, especially the correlations between the Mn in the welding fumes, Mn in the nails and outcome of the motor function tests. Another limitation might have been the fact that the data was collected over a short period of time, once at the beginning and once at the end of the month.

CONCLUSION

The higher statistical significant Mn concentrations in the nails of welders when compared to the non-exposed controls, provides the indication that Mn in welding fumes may have an influence on the deposition of Mn in nails although only a weak negative correlation was found between the Mn in the welding fumes and the Mn in the nails of the welders. The high statistical significant Mn concentration in nails of welders compared to controls also indicates that the Mn background in the human body is very low, confirming the fact that Mn in welding fumes may cause elevated nail Mn levels. Neither the duration of career welding nor the welders' age correlated with the Mn in the nails of the welders. This reveals that the deposition of Mn in nails, causing Mn toxicity, will not necessarily be influenced by long term exposure to Mn in welding fumes or by age. Using only the non-dominant hand during the Perdue pegboard tests showed a significant decrease in finger dexterity of the welders compared to that of the controls. Using the non-dominant hand and both hands simultaneously during the Perdue pegboard tests leaned towards a statistical significant decrease in finger dexterity of the welders compared to the controls. The moderate positive correlation observed between the Mn in the welding fumes and the number of errors that occurred during the mirror drawing coordination test done by the welders may be a result of welding fume-related neurotoxicity. A decrease in coordination occurs when exposure to Mn is increased. These results were obtained apart from the fact that welders have a possible training effect of fine motor control and hand-eye coordination. A decrease in the time of completion of the mirror drawing coordination tests done by the welders in comparison with the control subjects were shown, but no statistical significance was observed. Increasing the

study population as well as increasing the amount of respiratory sampling days between the beginning and end of the study is recommended for possible future studies.

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CHAPTER 4: CONCLUSIONS, RECOMMENDATIONS, LIMITATIONS AND FUTURE STUDIES

In this final chapter, the conclusions with regard to this study will be made with specific reference to the general aim, objectives and the postulated hypothesis. In an attempt to reduce manganese (Mn) exposure in welding fumes, recommendations will be provided to the chief executive officers and members of the management boards of the industrial companies. As a final point, the limitations of this study as well as possible future studies will be elaborated upon.

4.1 CONCLUSIONS

The personal respiratory exposure and biological load of Mn in welding fumes as well as the neurological influence it had on the 14 welders, was determined. The Mn exposure in the welding fumes varied from low concentrations (0.035 mg/m^3) to high concentrations (0.621 mg/m^3), but did not exceed the RHCS OEL-RL. The Mn in the nail clippings of the control subjects was 19.69-fold lower than that of the welders. These results indicate that nail clippings can serve as a reliable biomarker to determine Mn body burden.

No statistical significant correlation was found between Mn in the welding fumes and Mn in the nails of welders although the pooled Mn concentrations in the nails of the welders were statistical significantly higher ($p = 0.003$) than that of the non-exposed controls. This high statistical significant difference indicates that Mn in welding fumes may have an influence on the deposition of Mn in nails. The use of the non-dominant hand in the Perdue pegboard dexterity test was the only test that showed a significant decrease in finger dexterity of the welders compared to the controls ($p = 0.016$). The usage of both hands simultaneously also showed a significant decrease in finger dexterity of the welders compared to that of the control subjects but at a lower confidence level ($p = 0.012$). The results of the welders performing the mirror drawing coordination test showed a decrease coordination compared to the control subjects, although not significantly. The correlation between the Mn in the welding fumes and the number of errors that occurred during the coordination mirror drawing test done by the welders were strongly positive ($r = 0.612$; $p = 0.02$). A decrease in coordination occurred with an increase of Mn exposure. This indicates that the

welders may develop welding fume-related neurotoxicity although they are probably trained in fine motor hand movements and have good hand-eye coordination.

It was hypothesised that there would be a statistical significant correlation between the Mn respiratory exposure and the Mn found in the nails of the welders as well as a significant decrease in finger dexterity and coordination of the welders compared to the control group. This hypothesis was rejected due to the fact that there was no statistical significant correlation between the Mn respiratory exposure and the Mn found in the nails of the welders. The welders showed a statistical significant decrease in finger dexterity using their non-dominant hand while some of the other finger dexterity and coordination tests only leaned to statistical significance. The one test indicating the decrease in finger dexterity is insufficient to comply with the fact that the hypothesis stated that there would be a significant decrease in finger dexterity and coordination of the welders compared to that of the control group.

Brown *et al.* (2012) stated that it is safe to assume that individuals never know enough, or at least don't know all that there is to know. Not wearing any respiratory equipment will contribute to the welders developing adverse health effects in the future. Although adverse effects did not stand out in this study, future studies done on larger populations of welders may indicate more adverse effects supported by existing literature. The best way to protect the welders' health, regardless of what the outcome of the measurements is, is to eliminate or minimize the Mn exposure to the lowest possible degree.

4.2 RECOMMENDATIONS

Recommendations related to the results of the Article in Chapter 3 will be provided in the subsequent text. The recommendations apply to all 3 welding facilities. These recommendations will be made according to the hierarchy of control starting with the engineering controls (general ventilation and/or local ventilation) recommendations followed by the administrative controls and Personal Protective Equipment (PPE) recommendations. The recommendations are in no specific sequence.

Engineering controls

Recommendation 1: The measurement of natural as well as mechanical ventilation in a welding facility is of utmost importance. The environmental regulations for workplaces state that every workplace needs to be ventilated either by natural or mechanical means to ensure that the air breathed by the employee does not endanger his health or safety (Environmental regulations for workplaces, 1987). The following needs to be taken into account when ventilation measurements are made: drafts through the welding facility, wind direction, shaft effects and the location of the windows and building itself. According to AWS (2009), natural ventilation (roof vents, open doors and windows) can be acceptable for welding operations if the contaminants are kept below the permissible limits.

Recommendation 2: Provide a cross draft of air to prevent welding fumes from entering the welders breathing zone. A minimum cross draft away from the welders breathing zone of 0.5 m/s will be sufficient to protect the welder against inhalation of welding fume particulates and ozone. Making use of a pedestal fan is generally adequate for this purpose. This process spreads the fumes to other areas of the workplace and may therefore rather be acceptable for external work or one-man operations (WTIA, 2001; AWS, 2009).

Recommendation 3: According to WTIA (2001) control measures needs to be taken to protect both the welder as well as other workers in the workplace. It is important that other workers are correctly positioned to avoid being exposed to the cross draft leaving the welding area.

Recommendation 4: The most appropriate control method is to minimize the fume generation at the source (Antonini *et al.*, 2011). Flynn and Susi (2010) concluded that a 31% decrease in Mn levels in welders occurred due to the implementation of local exhaust ventilation (LEV). This LEV system includes a capture device, ducting and a fan (AWS, 2009). To ensure that neither the welders nor the other workers in the welding facility are exposed, LEV (static or mobile hoods) can be installed at welding areas to capture the welding fumes at the source.

- Locate the hood as close as possible to the welding point to ensure that the correct capture velocity is accomplished for effective capturing of the fumes (Fig. 1 left).
- Use baffles to manipulate the airflow into the hood, causing a greater % hood capture velocity further away from the opening of the hood (Fig. 1 right).

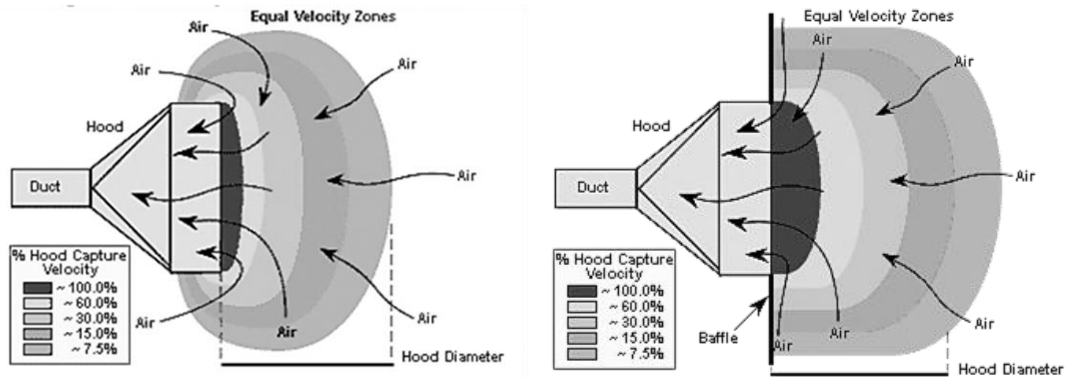


Figure 1: Capture velocities near a hood (left). Beneficial effect of side baffles on hood capture velocities (right).

- Position the hood to draw the fumes away from the welders breathing zone. A draft of air can also be blown over the back of the welder to ensure the fumes be drawn away from the breathing zone.



Figure 2: Extraction arm and crane extracting fumes away from the welder.

- A minimum capture velocity of 0.5 m/s, measured at the fume source, is required to protect the welder against particulate exposure generated near the arc.
- The higher the air velocities at the fume extractor, the greater the capture efficiency of the fumes. Gas shielded welding processes can tolerate air velocities up to 2 m/s.

- It is important that the exhaust fume from the LEV be filtered effectively, whether it is to be discharged into the welding facility or outside the welding facility. Properly filtered airflow may be recirculated. Whenever welding fumes are discharged outside the welding facility, the relevant environmental regulations should be followed as well as isolation from any air inlet to the welding facility needs to be done.
- Various extraction types exist each with advantages and disadvantages. It is recommended that the choice of extraction type made is according to the welding fume protection efficiency and the employers' financial ability.

Table 1: Extraction types used to reduce welding fume exposure
(WTIA, 2001).

Extraction type	Advantages	Disadvantages
Mobile hoods (e.g. articulated arms or magnetic hose kits) (Fig. 3)	<ul style="list-style-type: none"> - Long capture distance, less interference with worker; - High flow design will capture/extract high fume concentrations. 	<ul style="list-style-type: none"> - Has to be moved around in line with the work – and therefore may not always be used; - Every welder needs one, higher cost per welder.
On tool (e.g. fume extraction welding torch or on-tip soldering extraction) (Fig. 4)	<ul style="list-style-type: none"> - Automatically used when welding; - High pressure/low flow design uses small diameter hoses with easier design/installation requirements; - Generally has a lower cost per welder. 	<ul style="list-style-type: none"> - Adds weight to the tool/hand piece, reduces flexibility; - May not capture all fume (e.g. fume of sparks, residual fume when welding); - Requires careful set up to capture fume without stripping away shielding gases and regular service to maintain performance.
In-bench/fixed (e.g. downdraft or slot benches, solder fume enclosure systems) (Fig. 5)	<ul style="list-style-type: none"> - Automatically used when welding; - Combines work top/bench with extraction system; Various configurations available; - Suitable for high velocity fume applications. 	<ul style="list-style-type: none"> - Reduce flexibility; - Usually only suitable for small item work due to enclosure design; - Generally has a higher cost per welder.
Overhead canopy hoods (Fig. 6)	<ul style="list-style-type: none"> - Low cost 	<ul style="list-style-type: none"> - Rising fume travels through the breathing zone of the welders.

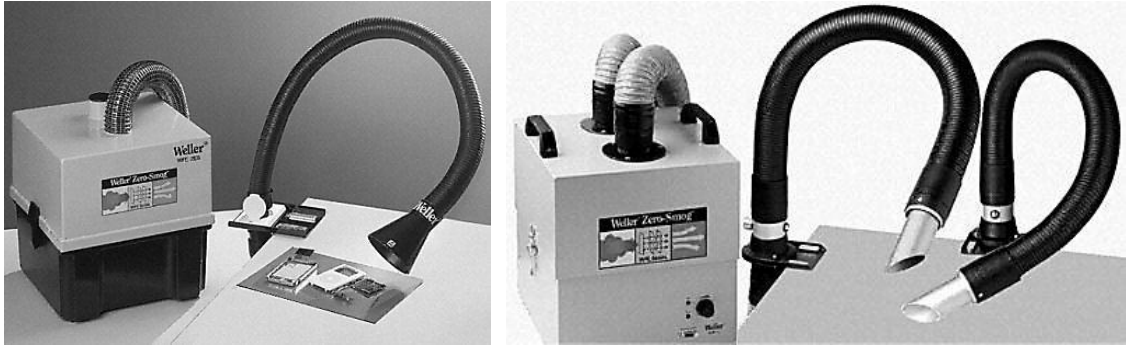


Figure 3: Mobile fume extraction system with one arm (left). Average cost: R10 332.99.
Mobile fume extraction system with two arms (right). Average cost: R17 769.22.

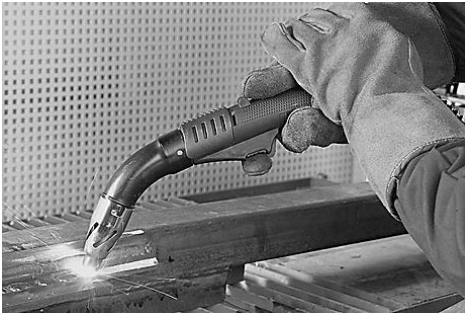


Figure 4: On torch welding fume extractor.



Figure 5: A fixed downdraft extractor.



Figure 6: Fume extraction through an overhead canopy hood.

Recommendation 5: Natural ventilation measurements should be collected before installing the hoods so as to ensure that the correct mechanical ventilation system is installed and no unnecessary expenses are incurred. The installation of hoods is expensive; more so in cases of faulty installation which may result from the lack of prior natural ventilation measurements. Said measurements will provide an indication regarding what type of mechanical ventilation system is needed and where this system would be most effective.

Recommendation 6: Whenever a welding facility makes use of exhaust fans, it is recommended that the exhaust fan blades are to be cleaned regularly. Ventilation measurements should be done to determine whether the fan provides sufficient extraction ventilation.

Administrative controls

Recommendation 1: According to Antonini *et al.* (2011), the Mn-percentage in welding fumes increases, while welding stainless steel at high welding voltages (30V). At lower voltages (25V), the electrode short circuits which keeps the temperature lower, causing a reduction in the amount of metal vaporization and subsequent re-condensation. Another study undertaken by Hovde and Raynor (2007) revealed that ultrafine particle concentrations increase more than three times at higher welding voltages during gas metal arc welding causing pulmonary toxicity. Although mild steel is used it is recommended that the welding process takes place at the same lower voltage (25V) as when welding stainless steel (Antonini *et al.*, 2011).

Recommendation 2: Ensure that the welders are adequately and comprehensively informed and trained on the following subjects:

- The content and scope of the regulations regarding welding fume exposure;
- The potential source of welding fume exposure;
- The potential health risks caused by welding fume exposure;
- The measures to be taken by the employer to protect the welder against any risk from welding fume exposure;

- The precautions to be taken by the welder to protect him against the health risks associated with welding fume exposure, including the wearing and usage of respiratory protective equipment and clothing;
- The necessity, correct use, maintenance and potential of safety equipment, facilities and engineering control measures provided;
- The necessity of personal air sampling and medical surveillance; and
- Obeying a lawful instruction given by the employer regarding –
 - The wearing of the PPE;
 - The wearing of monitoring equipment to measure personal exposure;
 - Information and training as given above.

Recommendation 3: Provide supervision and enforcement to ensure that the welders wear their PPE. It is also recommended that more PPE mandatory signs be added in the workshop.

Recommendation 4: Ensure that all control equipment and facilities provided are maintained in good working condition.

Recommendation 5: Take welding fume measurements more often. According to RHCS (1995) air monitoring for welding fumes should be carried out at least every 24 months by an approved inspection authority (AIA).

For further information regarding duties and responsibilities of the employer and employee refer to RHCS (1995).

PPE

Recommendation 1: It is recommended that the correct respiratory protection equipment is worn, either air-purifying or supplied air. For exposures $< 10\text{mg}/\text{m}^3$, such as this situation, a respirator equipped with an N95 or R95 filter (including N95 and R95 filtering facepieces) can be used, except quarter-mask respirators. The following filters may also be used: N99, R99, P99, N100, R100, P100 (NIOSH, 2010). The most affordable respirator which can be used is a half-facepiece respirator with replaceable N95 particulate filters (Fig. 7), or a disposable half-facepiece N95 particulate filter respirator (Fig. 8). According to Frick *et al.* (2011), intracellular oxidative stress and alveolar epithelial cell apoptosis occurs due to the

uptake of Mn_3O_4 nanoparticles. It may be advisable to use a respirator equipped with a R99 or R100 filter to ensure capturing of these nanoparticles. The reusable respirators are suitable for more prolonged use although it has the same protection factor as disposables, requires a maintenance program as well as training before use. The disposables are lightweight and maintenance free. It does however also require training before use.



Figure 7: Half-facepiece respirators with replaceable N95 (left) and P100 particulate filters (right). Average cost for a 3M half-facepiece respirator 6000 series: R216.79. The filters range from R857.51 to R1805.27 per box of 8.

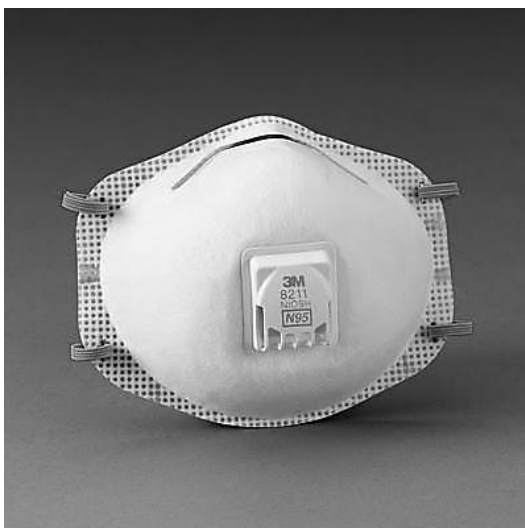


Figure 8: A disposable half-facepiece N95 particulate respirator also referred to as filtering facepiece respirator. Average cost for a disposable 3 M half-facepiece particulate respirator specifically for welding: R94.33.

Recommendation 2: For the greatest welding fume protection and reduction in health effects, provide each welder with a 3M Speedglas™ welding shield (Fig. 9) and Adflo™ powered air respirator (Fig. 10). The Speedglas™ is the only welding shield with exhaust vents. The auto-darkening welding filter provides a clear, protected view under all lighting conditions. The shield also has an extra-large viewing area which expands the welder's field of vision. This shield is suitable for all types of arc welding as well as providing eye protection when non-welding tasks takes place. It is light weighted and comfortable causing faster and improved work performance.



Figure 9: Speedglas™ welding shield worn during welding (left), non-welding tasks (middle) and the vision of the welding shield from the inside (right). Cost of Speedglas™ welding shield: From R1986.60.

The Adflo™ powered air respirator consists of a battery powered motor unit which causes air to travel through pre-filter and particle filter in order to minimize respiratory hazards. Subsequently it directs the air via air hose into the welding shield. This air in conclusion with the sealed welding shield keeps non-filtered air outside the shield. The respirator has a higher protection factor and can be worn for long periods, causing no breathing resistance. The battery does require charging and replacement. A maintenance program and training before use is also required. This respirator is portable, lightweight and comfortable with a battery that last for a full 8-hour shift.

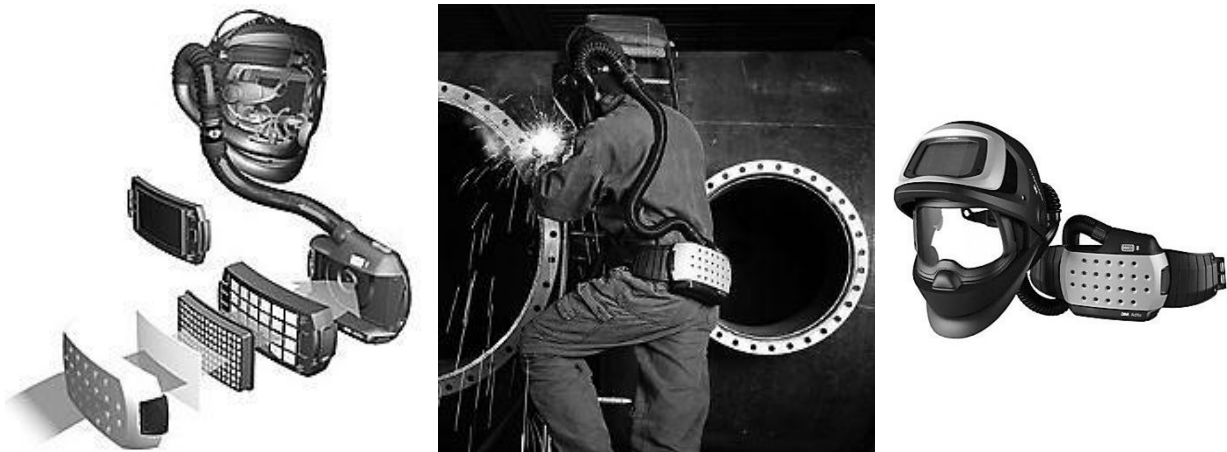


Figure 10: Adflo™ powered air respirator filtering system (left), welding with the powered air respirator (middle) and Speedglas with Adflo powered air respirator (right). Cost of Adflo™ powered air respirator: From R4 456.78.

Recommendation 3: It is important to note that each welder receives his own personal respirator which is able to control the welding fume exposure below the OEL. Provide each welder with a respirator storage container for periods when it is not in use in order to prevent external contamination.

Recommendation 4: Before any respirator can be worn, each worker needs to undergo training on the correct usage of the specific respirator as well as respirator fitting tests. These tests consist of qualitative as well as quantitative procedures. The qualitative tests include using test mediums such as isoamyl acetate, saccharin, Bitrex™ or irritant smoke. If one of these mediums can be smelled then the fitting test is negative and the respirator is not suitable for the worker. The quantitative test includes measuring the actual leakage of the test gas inside the respirator. For the complete fit testing procedures refer to OSHA (2004a).

Recommendation 5: Replace the respirator and its filters according to the OSHA requirements for change schedules and cartridge service life (OSHA, 2004b). It is important to note that temperature, humidity, air flow through the filter, the work rate, and the presence of other potential interfering chemicals in the work place can influence the service life of the respirator. The service life of the filters can also be influenced by factors and needs to be taken into account when determining the

change schedule. These factors include environmental conditions, breathing rate, filtering capacity, and the amount of contaminants in the air.

At the end it would be more cost effective and safer to the welders to install mechanical ventilation systems if there are many welders. Replacing disposable respirators, filters of reusable respirators and reusable respirators of many welders will be a greater expenditure in years of times than installing LEV once. Another possibility is to provide each welder with a good protective welding shield containing a powered air respirator if there are only a few welders. This is a more expensive method of protection but would be an investment for the future.

4.3 LIMITATIONS

The following limitations regarding the exposure of welders to Mn in welding fumes have been identified:

- Data was only collected twice, once at the beginning of the study and again at the end of the study.
- The evaluation was done on a small exposure population group (n = 14).
- There was a lack of detailed and accurate exposure information regarding all the aspects of the welding exposure including:
 - The processes and types of rods/wires used,
 - Fume and Mn concentrations,
 - Duration and frequency of welding, and
 - Information on exposure to other neurotoxicants in the workplace.
- Welding requires adequate hand steadiness and manual dexterity, making it difficult to find the appropriate control group for the welders.
- Welding for many years improves the welders' training effects, causing an underestimation of the adverse neuromotor effects due to Mn exposure.

4.4 FUTURE STUDIES

- The measurement of larger populations of welders would improve the statistical power of data and consequential conclusions.
- It would be beneficial if the correlation between personal monitoring and biological monitoring could be done over a longer period of time. Increasing

the amount of airborne welding fume measurements from the beginning to the end of the study would also be advisable.

- The measurement of workers other than welders in open welding facilities could also be taken into consideration when measuring welding fume.
- The analysis of all the different metals released from the welding fumes, causing health impairment, can be done in future.
- In the future more motor function tests can be done in a similar study to determine the deviation of fine motor dexterity and coordination of welders. These tests may include hand steadiness/hand tremor, finger tapping or postural sway.

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CHAPTER 5: APPENDICES

Appendix A



November 7, 2012 NORTH-WEST UNIVERSITY
YUNIBESITHI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

To whom it may concern

I, Kalienka Marx (21276056), declare that I have done the proof reading as well as the grammar editing for Ms. M. Ferreira (21235988) for her mini dissertation entitled **Exposure of welders to Manganese in welding fumes.**

A handwritten signature in black ink, appearing to read 'Kalienka'.

Kalienka Marx

Interpreter and Translator (Physiology)

North-West University

084 089 7644

Appendix B



NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

Prof/Dr/Mr/Me

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: (018) 299-4900
Faks: (018) 299-4910
Web: <http://www.nwu.ac.za>

ETHICS APPROVAL OF PROJECT

Ethics Committee

Tel +27 18 299 4850
Fax +27 18 293 5329
Email Ethics@nwu.ac.za
2012/11/01

This is to certify that the next project was approved by the NWU Ethics Committee:

<p><u>Project title :</u> Exposure of welders to manganese in welding fumes</p> <p><u>Project leader:</u> Mr. Petrus Laubsher</p> <p><u>Ethics number:</u> NWU-00043-12-A1</p> <p><small><u>Status:</u> S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation</small></p> <p>Expiry date: 2017/10/15</p>
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The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

The formal Ethics approval certificate will be sent to you as soon as possible.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Me. Marietjie Halgryn'.

Me. Marietjie Halgryn
NWU Ethics Secretariate