

Dermal and respiratory exposure to nickel in a packaging section of a base metal refinery

HJ Claassens

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Supervisor: Prof JL du Plessis

Co-supervisor: Prof FC Eloff

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Preface

This mini-dissertation is submitted in an article format in accordance with the requirements of the journal *Annals of Occupational Hygiene*. This journal requires that references should be listed in alphabetical order by name of first author, using the Vancouver Style of abbreviation and punctuation.

Author's Contribution

The study was planned and executed by a team of researchers. The contribution of each researcher is listed below:

Name	Contribution
Mr.H.J Claassens	<ul style="list-style-type: none">• Designing and planning of the study;• Literature searches, interpretation of data and writing of article;• Execution of all monitoring processes.
Prof. J.L du Plessis	<ul style="list-style-type: none">• Supervisor;• Assisted with approval of protocol, interpretation of results and documentation of the study;• Giving guidance with scientific aspects of the study.
Prof. F.C Eloff	<ul style="list-style-type: none">• Co-Supervisor;• Assisted with designing and planning of the study, approval of protocol.

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

I declare that I have approved the above mentioned 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 HJ Claassens's M.Sc (Occupational Hygiene) mini-dissertation.

Prof. J.L du Plessis

(Supervisor)

Prof. F.C Eloff

(Co-Supervisor)

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Abstract

Title: Dermal and respiratory exposure to nickel in a packaging section of a base metal refinery.

Nickel is one of the most commonly known sensitizers and has been classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen to humans (group 2B). Workers at a South African base metal refinery packaging area are potentially exposed to many hazardous chemicals that include nickel.

Aims and Objectives: The aim and objectives of this study were to assess dermal and respiratory exposure of workers exposed to nickel in a packaging section at a South African base metal refinery and to assess the change in skin barrier function during a work shift by measuring percentage change in trans epidermal water loss (TEWL), skin hydration and skin surface pH. Skin health was established with a skin questionnaire. Surfaces that workers may come into contact with were also assessed.

Method: Respiratory and dermal exposure assessment was done concurrently. Respiratory exposure was assessed and analysed by using the National Institute for Occupational Safety and Health (NIOSH) method 7300. The Institute of Occupational Medicine (IOM) inhalable aerosol sampler was used for personal air sampling. The TEWL index, skin hydration and skin surface pH of the index finger, palm, forearm and forehead were measured before and at the end of the shift with a Derma Measurement Unit, EDS 12 and Skin-pH-Meter® pH 905. These measurements were reported as percentage change in skin barrier function during the shift. Dermal exposure samples were collected with Ghostwipes™ from the index finger and palm of the dominant hand before, during and at the end of the shift, while samples from the forearm and forehead were only collected before and after the shift. Surface sampling was collected and all wipes were analysed for nickel according to the NIOSH method 9102, using inductively coupled plasma-atomic emission spectrometry.

Results: Respiratory exposure for the whole group of workers in a packaging section was well below the eight hour Time Weighted Average (TWA) respiratory Occupational Exposure Limit (OEL) of 0.5 mg m^{-3} for nickel. Dermal nickel loading was detected for all the job categories on all the anatomical areas even before the shift had commenced. During the shift more nickel was detected on the index finger and palm of the hand. Levels on the forearm and forehead were much lower in comparison with the index finger and the palm of the hand. Workplace surfaces, which workers may come into contact with on a daily basis, were also contaminated with nickel. Forklift drivers showed high exposure on the index finger and palm of their hands, and this can be attributed to them not wearing any gloves for hand protection. An increase in percentage change for TEWL was seen for most of the job

categories on all anatomical areas measured during the shift. Percentage change in skin surface pH and skin hydration varied among job categories.

Conclusion: The research addressed the problem statement, with the stated objectives. It was hypothesised that workers at a packaging section of a base metal refinery are exposed to quantifiable levels of nickel through the dermal exposure route. The hypothesis was accepted and control measures together with future studies were recommended.

The results confirmed that all workers at a base metal refinery are exposed to quantifiable levels of nickel through the dermal exposure route. Dermal exposure was evident on all anatomical areas for all job categories before the shift had commenced. Personal protective equipment was provided to all employees, but forklift drivers did not wear gloves when operating the forklift. Respirable exposure to nickel was below the OEL. Changes in TEWL and to a lesser extent skin hydration, suggest a deterioration in skin barrier function during the shift. Forklift drivers as well as plate washers may be the highest risk job categories in developing allergic contact dermatitis. Several measures to lower respiratory and dermal exposure to nickel are also recommended.

Keywords:

Respirable, skin exposure, skin hydration, TEWL, skin surface pH, skin barrier function, hazardous chemicals.

Opsomming

Titel: Dermale en respiratoriese blootstelling aan nikkel in 'n verpakkingsaanleg van 'n nie-edel metaalraffinadery.

Nikkel is 'n alombekende sensitiseerder in die industrieë en is ook geklassifiseer deur die Internasionale Agentskap vir Navorsing vir Kanker (IARC) as 'n moontlike menslike karsinogeen. Werkers by 'n verpakkingsaanleg van 'n Suid-Afrikaanse nie-edel metaalraffinadery word aan verskeie gevaarlike chemiese substansies blootgestel waarvan nikkel een is.

Doelstelling en doelwitte: Die navorsingsdoelstelling en -doelwitte van hierdie studie was om respiratoriese en dermale blootstelling te assesseer, asook die verandering in die velgrensfunksie gedurende die werkskof, deur velhidrasie, trans epidermale water verlies (TEWV) en veloppervlak pH van werkers wat aan nikkel by 'n verpakkingsaanleg by 'n nie-edel metaalraffinadery blootgestel word, te bepaal. Vel gesondheid was geïdentifiseer deur gebruik te maak van 'n vel vraagstuk. Die oppervlaktes waarmee werkers moontlik daaglik in aanraking kan kom, is ook geassesseer.

Metode: Die assessering van respiratoriese en dermale blootstelling is gelyktydig gedoen. Respiratoriese blootstelling is volgens National Institute of Occupational Safety and Health (NIOSH) metode 7300 geëvalueer. Die monsters is geneem deur van die Institute of Occupational Medicine (IOM) se inasembare monsternemer gebruik te maak. Die TEWL-indeks en velhidrasie is op die indeksvinger, palm, voorarm en voorkop aan die begin en einde van die skof met 'n Derma Meetinstrument, EDS 12, gemeet. Veloppervlak pH is met 'n Skin-pH-Meter[®] pH 905 op die indeksvinger, palm en voorkop, aan die begin en einde van die skof gemeet. Die metings is as 'n persentasie verandering in velgrensfunksie gerapporteer. Dermale blootstelling aan nikkel is met Ghostwipes[™] as 'n verwyderingsmetode bepaal. Die indeks-vinger, palm, voorarm en voorkop is voor die aanvang van 'n skof, voor pouse 1 en pouse 2 en aan die einde van die skof gemeet. Monsters is op werksoppervlaktes waarmee werkers moontlik in aanraking sal kom met Ghostwipes[™] versamel. Velveeglappe tesame met respiratoriese monsters is vir nikkel volgens NIOSH-metode 9102, wat gebruik maak van Plasma-Atoom Emissie Spektrometrie, geanaliseer.

Resultate: Respiratoriese blootstelling vir die hele groep werkers in die verpakkingsaanleg was baie laer as die agt ure tydbeswaarde respiratoriese beroeps blootstellingsdrempel van 0.5 mg m^{-3} vir nikkel. Dermale nikkel is op alle anatomiese areas vir al die werkskategorieë gevind nog voordat die skof begin het. Gedurende die skof is nikkel op die indeksvinger en

palm van die hand gevind. Nikkel vlakke op die voorarm en voorkop was laer in vergelyking met die indeksvinger en palm van die hand. Werksoppervlaktes was ook deur nikkel gekontamineer. Vurkhyserbestuurders het hoë blootstelling op die indeksvinger en handpalm getoon, wat daaraan toegeskryf kan word dat hulle nie handskoene vir beskerming gedra het nie. 'n Verhoging in die persentasie verandering vir TEWL op al die anatomiese areas is by die meeste werkskategorieë waargeneem. Die persentasieverandering in veloppervlak pH en velhidrasie het gewissel tussen die onderskeie werkskategorieë.

Gevolgtrekking: Die navorsingstudie het die probleemstelling aangespreek en die gestelde doelwitte is bereik. Die hipotese in die studie, naamlik dat werkers in 'n verpakkingsaanleg van 'n nie-edel metaalraffinadery blootgestel word aan kwantifiseerbare vlakke van nikkel deur die dermale roete van blootstelling is getoets. Die hipotese is aanvaar. Ekstra beheermaatreëls en toekomstige studies is aanbeveel.

Die resultate het bevestig dat alle werkers van 'n nie-edel metaalraffinadery blootgestel word aan kwantifiseerbare vlakke van nikkel deur die dermale roete van blootstelling. Dermale blootstelling was te vinde op alle anatomiese areas vir alle werkskategorieë, voor die werkskof begin het. Persoonlike beskermende toerusting word aan alle werkers verskaf, maar vurkhyserbestuurders het glad nie handskoene gedra terwyl hulle die vurkhyser bestuur het nie. Die respiratoriese blootstelling aan nikkel was ver onder die beroepsblootstellingsdrempel. Die persentasie verandering in velgrensfunksie het op moontlike afname in velgrensfunksie gedui gedurende die skof. Vurkhyserbestuurders en plaatwassers mag moontlik die hoogste risiko werkskategorieë vir die ontwikkeling van allergiese kontakdermatitis wees. Verskeie beheermaatreëls vir die verlaging van dermale en respiratoriese blootstelling aan nikkel is aanbeveel.

Sleutelwoorde: Respiratoriese blootstelling, velblootstelling, velhidrasie, TEWL, velbeskermingsfunksie, gevaarlike chemiese substansie.

Table of contents:

Preface.....	ii
Author's Contribution.....	iii
Acknowledgements.....	iv
Abstract.....	v
Opsomming.....	vii
Table of Contents.....	ix
List of Figures.....	xiii
List of Tables.....	xiv
List of Symbols and Abbreviations	
Symbols.....	xv
Abbreviations.....	xv
CHAPTER 1 - INTRODUCTION	
1.1 Overview.....	2
1.2 Aim.....	4
1.2.1 Objectives.....	4
1.3 Hypothesis.....	5
1.4 References.....	6
CHAPTER 2 - LITERATURE STUDY	
2.1 Introduction.....	10
2.2 Properties of nickel and nickel compounds and it's uses.....	10
2.3 Exposure to nickel and nickel compounds.....	12
2.4 Respiratory exposure.....	13
2.4.1 The Respiratory tract.....	13
2.4.2 Particle deposition in the respiratory tract.....	13
2.4.2.1 Inertial Impaction.....	13
2.4.2.2 Sedimentation.....	14

2.4.2.3 Diffusion.....	14
2.4.3 Clearance of particles.....	14
2.4.3.1 Upper respiratory or nasal clearance.....	15
2.4.3.2 Tracheobronchial clearance.....	15
2.4.3.3 Pulmonary clearance.....	15
2.4.4 Respiratory exposure studies.....	15
2.5 Dermal exposure.....	16
2.5.1 The Skin.....	16
2.5.1.1 Histology of the skin.....	17
2.5.1.2 Functions of the skin.....	18
2.5.1.3 Skin barrier function.....	18
2.5.1.4 Parameters and other factors influencing skin barrier function.....	19
2.5.1.4.1 Trans Epidermal Water Loss.....	19
2.5.1.4.2 Skin hydration.....	20
2.5.1.4.3 Skin surface pH.....	20
2.5.1.4.4 Other factors influencing skin barrier function.....	21
2.5.1.4.4.1 Endogenous factors.....	21
2.5.1.4.4.2 Exogenous factors.....	22
2.5.1.4.4.3 Environmental and measurement factors.....	23
2.6 Human health effects of nickel.....	27
2.6.1 Allergic contact dermatitis.....	27
2.6.2 Respiratory effects.....	28
2.6.3 Carcinogenesis.....	28
2.7 References.....	29

CHAPTER 3 - ARTICLE

Abstract.....	44
Introduction.....	46
Methodology	
Workplace Description.....	48
Respiratory exposure sampling.....	49
Dermal exposure sampling.....	49
Surface sampling.....	50
Percentage change in skin barrier function.....	50
Skin condition questionnaire.....	51
Ethical aspects.....	51
Statistical Analysis.....	51
Results.....	51
Respiratory exposure.....	51
Dermal exposure.....	53
Surface exposure.....	54
Change in skin barrier function.....	54
Skin questionnaire.....	56
Discussion.....	57
Conclusion.....	61
References.....	63

CHAPTER 4 - CONCLUDING CHAPTER

4.1 Introduction.....	70
4.2 Summary of main findings and conclusion.....	70
4.3 Challenges of this study.....	71
4.4 Future investigations.....	71
4.5 Occupation Hygiene Recommendation.....	72

4.5.1 Engineering Control.....	72
4.5.2 Administrative Control.....	73
4.5.3 Respiratory Protection.....	73
4.6 References.....	74
English Language Editing Certification	75

List of Figures:

CHAPTER 3

Figure 1. Full-shift dermal exposure to nickel for the (A) Index finger, (B) Palm, (C) Forearm and (D) Forehead (mean \pm SD).....54

Figure 2. Percentage change in a) Skin hydration, b) TEWL and c) Skin surface pH from beginning to end of work shift (mean \pm SD).....56

List of Tables:

CHAPTER 2

Table 1:

Physical and Chemical Properties of Nickel 11

Table 2:

Comparison between different Occupational Exposure Limits for nickel compounds (mg m^{-3})
..... 12

Table 3:

Endogenous, exogenous and environmental factors affecting skin surface pH, TEWL and
skin hydration 24

CHAPTER 3

Table 1:

TWA respiratory nickel exposure (mg m^{-3}) of processors in the nickel packaging area..... 52

List of Symbols and Abbreviations

Symbols

%	Percentage
±	Plus-minus
µg	Micrograms
µg cm ⁻²	Micrograms per square centimetre
mg	Milligram
mg cm ⁻²	Milligram per square centimetre
mg m ⁻³	Milligram per cubic metre
pH	Hydrogen ion concentration

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
FFP2	Filtrated Face piece (class 2)
HSDB	Hazardous Substances Data Bank
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
IOM	Institute of Occupational Medicine
MDHS	Methods for the Determination of Hazardous Substances
MHS	Mine Health and Safety
OEL	Occupational Exposure Limit
NIOSH	National Institute for Occupational Safety and Health
PGM	Platinum group metals
TEWL	Transepidermal Water Loss
TWA	Time Weighted Average

CHAPTER 1

INTRODUCTION

1.1 Overview

Exposure to nickel and nickel compounds is extremely detrimental to human health as all nickel compounds are to be considered carcinogenic to humans (group 1). This includes cancers of the lung, nasal cavity and paranasal sinuses (IARC, 2012). Metallic nickel is classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen to humans (group 2B) (IARC, 1990). The IARC reported elevated risk of lung and nasal cancers of workers involved in a variety of nickel refining and ore smelting processes, which included high-temperature processing of nickel matte, nickel-copper matte and electrolytic refining (IARC, 2012).

Aside from nickel's strong carcinogenic properties, especially via respiratory exposure, it is also the most common contact allergen in the general population and causes type IV delayed hypersensitivity reactions (Vahter *et al.*, 2007). Nickel contact dermatitis develops locally with intense itching, and spreads to other sites by scratching. This dermatitis can be chronic and severe (Sullivan and Krieger, 2001).

Even though Occupational Hygiene traditionally focused more on the respiratory tract as a primary route of exposure in terms of potential toxicity, rather than dermal and ingestion exposure (Semple, 2004; Cherrie *et al.*, 2006), a paradigm shift has taken place, and exposure to hazards via dermal routes is enjoying more attention. In recent years, occupational hygienists anticipated and advised the general worker population that a decreased integrity of the skin barrier may increase dermal penetration of chemicals (Nielsen, 2005). The skin is the largest organ in the body and it serves as a protective barrier against substances that can have deleterious effects when absorbed (Agache, 2004; Sand *et al.*, 2009). It is a complex and integrated membrane and, with the help of several interrelated mechanisms, percutaneous absorption of metals such as nickel can occur. This absorption is influenced by a number of exogenous and endogenous factors such as dose, vehicle, molecular volume, age of the skin, and anatomical site (Hostynek, 2003). Kezic and Nielsen (2009) demonstrated that limited damage to skin increases the permeability coefficient drastically, as well as the total percutaneous penetration of chemicals. There are some studies that have shown that compromised skin is a far less effective barrier against percutaneous penetration of chemicals when compared to uncompromised skin (Nielsen, 2005; Jakasa *et al.*, 2006; Larese Filon *et al.*, 2009).

Du Plessis *et al.* (2010) reported on the actual means of measurement of skin barrier function upon exposure, and the subsequent use thereof in combination with dermal exposure results, while other studies only reported on dermal exposure. There are three distinct parameters that can give an indication of the skin barrier function namely; skin hydration and trans epidermal water loss (TEWL) and skin surface pH. Skin hydration reflects the moisture level of the skin's surface, while TEWL reflects the total amount of water vapour lost through the skin in the absence of thermal sweating. Thus, TEWL is the actual water evaporative rate, and is accepted as a dependable indicator of epidermal barrier homeostasis (Rawlings *et al.*, 2008). Three main closely interconnected concepts may be considered in relation to skin surface pH: the "acid mantle", the natural moisturizing factor (NMF) and the buffering capacity of the skin (Parra & Paye, 2003). The pH of the skin also plays a significant role in the skin barrier homeostasis and gives rise to the "acidic mantle" (Rippke *et al.*, 2002; Parra & Paye, 2003). Not only does the natural moisturizing factor (NMF) help in maintaining the water retention capacity of the skin, but also have a relevant buffering capacity for the water in the corneocytes. The maintenance of the stratum corneum physiological acidity and elasticity of the skin may be facilitated by the buffering capacity (Chikakane & Takahashi, 1995; Parra & Paye, 2003). Ionization of compounds in the stratum corneum is probably influenced by the acidic pH of the skin surface, however, the buffering capacity of the stratum corneum may enhance this process and regulate the stratum corneum pH gradient (Warner *et al.*, 1995, Parra & Paye, 2003). The structure of the stratum corneum varies significantly between anatomical positions and consequently these differences play an important role in the permeability of the skin (Rice & Mauro, 2008). It is well known that compromised skin is associated with an increase in TEWL, which is an indication of impaired skin barrier function (Mündlein *et al.*, 2008) and is frequently correlated with low hydration of the stratum corneum (Proksch *et al.*, 2008). Sweating from physical, thermal and emotional mechanisms increases skin hydration and TEWL values (Pinnagoda *et al.*, 1989; Goh, 2006; Du Plessis *et al.*, 2013), but can be controlled by allowing adequate acclimatization of the workers to the environment and performing measurements under controlled environmental conditions (Pinnagoda *et al.*, 1990; Berardesca, 1997; Rogiers, 2001; Du Plessis *et al.*, 2013). Dermatitis is associated with increased TEWL (Jakasa *et al.*, 2006). When the skin barrier is impaired the pH increases and activities surrounding the increased pH, such as cutaneous inflammation occur (Rippke *et al.*, 2002).

According to the Occupational Hygiene Regulations as stipulated in the South African Mine Health and Safety Act, 1996 (Act no. 29 of 1996), the current eight hour time weighted average

Occupational Exposure Limit (8h TWA-OEL) for soluble, inorganic nickel compounds is 0.1 mg/m³ and insoluble compounds 0.5 mg/m³ with no skin or sensitiser notation.

A recent study done by Hughson *et al.* (2010) reported dermal and inhalation exposure to nickel in nickel production and primary user industries in a developed country. Dermal exposure was measured by using moist wipes to recover nickel from certain areas of the skin and analysed for soluble and insoluble nickel. Du Plessis *et al.* (2010) reported dermal exposure to nickel and what the effect of the work environment have on skin barrier function in an electro-winning plant (tank house) of a base metal refinery in South Africa.

This study will focus on respiratory and dermal exposure at a packaging area of a base metal refinery in South Africa. The percentage change in skin parameters (TEWL, skin hydration and skin surface pH) during a work shift will be assessed in accordance to international guidelines (Du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013) and workers will fill out a skin questionnaire.

1.2 Aim

The aim of this study was:

- To evaluate respiratory and dermal exposure and change in skin barrier function during a work shift of workers exposed to nickel at a packaging section of a base metal refinery.

1.2.1 Objectives

The objectives of the study were:

- To assess the respiratory and dermal exposure of workers exposed to nickel involved in packaging at a base metal refinery with the use of personal air sampling methods and Ghostwipes™ respectively.
- To assess the percentage change in skin parameters (TEWL, skin hydration and skin surface pH) during a work shift in accordance to international guidelines, and workers completed a skin questionnaire.
- To assess the surfaces for nickel contamination, that workers may come into contact on a daily basis by taking surface wipe sampling using Ghostwipes™

1.3 Hypothesis

The following hypothesis is postulated:

Nickel sheets are manually handled by the workers. The workers may also come into contact with surfaces that are potentially exposed to nickel on a daily basis. Therefore, it is hypothesised that the workers at a packaging section of a base metal refinery are exposed to quantifiable levels of nickel through the dermal exposure route.

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CHAPTER 2

LITERATURE OVERVIEW

2.1 Introduction

Nickel was discovered unintentionally in 1751 by Baron Axel Frederick Cronstedt, who extracted it from a mineral called niccolite. His intention was to extract copper but his efforts produced a white substance rather than the reddish substance he expected to retrieve. He named the new metal “kupfernickel” that translates from German for that epoch to: “Devil’s copper” (Encyclopedia Britannica, 2012).

Nickel is no exception when it comes to a metal causing adverse health effects. It is only one of many chemical stressors found at a base metal refinery to which employees are exposed. The respiratory tract has traditionally been seen as the main target organ (Semple, 2004), and subsequently the main focus of occupational hygiene is respiratory exposure of nickel and other chemical stressors, however, the potential health effects following skin exposure cannot be ignored.

In this chapter the properties and uses of nickel, dermal exposure in general, functions of the skin, skin barrier function and the parameters influencing skin barrier function, respiratory exposure and its general health effects associated with dermal and respiratory exposure to nickel will be discussed.

2.2 Properties of nickel and nickel compounds and its’ uses.

Nickel ore is mined in over 23 countries (NiDI, 2011). More than 12 million tons of nickel, that represents 8.5 per cent of the world’s nickel reserves, are located in South Africa’s Bushveld Igneous Complex (Chamber of Mines South Africa, 2011).

Nickel is a lustrous, natural occurring, silvery–white metallic element. It is the 5th most common element on earth and occurs extensively in the earth’s crust. It is also an extremely important commercial element (Liu *et al.*, 2008; NiDI, 2011). Since its discovery, nickel and its compounds have become widely used in industries (Kasprzak *et al.*, 2003). The prevalent use of nickel is alloying with other materials where it adds strength and corrosion resistance due to its physical and chemical properties over a wide range of temperatures (Winder, 2004; Liu *et al.*, 2008). Other uses of nickel include those of rechargeable batteries, electroplating, welding and the manufacturing of jewellery and coins (Liu *et al.*, 2008). In Table 1, the physical and chemical properties of nickel is presented.

Table 1. Physical and Chemical Properties of Nickel (HSDB, 2012).

Characteristic	Value
Atomic number	28
Molecular weight	58.71
Density	8.90 g/cm ³ at 25 °C
Melting point	1453 °C
Boiling point	2730 °C
Curie temperature	253 °C

In the Occupational Hygiene Regulations as stipulated in the South African Mine Health and Safety Act, 1996 (Act no. 29 of 1996), the current eight hour time weighted average Occupational Exposure Limit (8h TWA-OEL) for soluble, inorganic nickel compounds is 0.1 mg m⁻³ and insoluble compounds 0.5 mg m⁻³ with no skin or sensitizer notation. In Table 2 a comparison is drawn between the South African Mine Health and Safety Act (MHSA) and some international exposure limits to nickel.

Tabel 2. Comparison between different Occupational Exposure Limits for nickel compounds (mg m⁻³).

Nickel Compound	MHSA (MHSA, 1996)	ACGIH(TLV) (ACGIH, 2013)	NIOSH(REL) (NIOSH, 2011)	HSE (WEL) (HSE, 2005)
Metallic Nickel	0.5	1.5	0.015	0.5
Insoluble Nickel	0.5	0.2	0.015	0.5
Soluble Nickel	0.1	0.1	0.015	0.1
Nickel subsulfide	0.1	0.1	-	-

South African standard - MHSA: Mine Health and Safety Act, Act 29 of 1996, Table 2 of Regulation 22.

United States of America standards - ACGIH: American Conference of Governmental Industrial Hygienists; TLV: Threshold Limit Value; NIOSH: National Institute for Occupational Safety and Health; REL: Recommended exposure Limit.

United Kingdom standard - HSE: Health and Safety Executive. WEL: Workplace Exposure Limit.

2.3 Exposure to nickel and nickel compounds

The high utilization of nickel products unavoidably leads to occupational and environmental pollution. In occupational settings, exposure to nickel and its compounds occurs mainly during electroplating, welding and nickel refining. Insoluble nickel species, such as nickel sulfide, nickel oxide and metallic nickel contained in fumes and dust, are the most common airborne nickel exposure in the workplace (ATSDR, 2005; DEPA, 2008; Liu *et al.*, 2008). For this study two main routes of exposure to nickel were identified: (1) Inhalation of airborne nickel and deposition in the respiratory tract, thus respiratory exposure (2) and nickel deposition of airborne nickel

coming in contact with the skin giving rise to dermal exposure. To follow is a brief discussion on respiratory and dermal exposure to nickel.

2.4 Respiratory exposure

Inhalation is the primary and most important occupational route for nickel-induced toxicity in the workplace and increases the risk for respiratory cancer (Oller, 2002; Goodman *et al.*, 2011). Nickel and its compounds that become airborne can easily be inhaled and deposited in the respiratory tract. The chemical and physical properties of nickel and nickel compounds strongly influence its' bioavailability and toxicity (Oller, 2002).

2.4.1 The respiratory tract

The respiratory tract can be divided into two systems, the upper and lower airway passages. The upper airway passage is a collection of passages that extends from the nares and mouth through the nasopharynx and oropharynx down to the vocal cords in the larynx. The upper airway passage functions include warming and humidifying the passing air, filtering particulate matter, and preventing aspiration during swallowing (Jaeger & Blank, 2011). The lower airway passage extends from the trachea where it is divided into the left and right bronchioles which enter the left and right lungs respectively. Its primary function is to conduct air from the upper airway to the alveoli. The alveoli are tiny air sacks where gas exchange occurs and covers an area of a tennis court packed into two lungs. With the large surface area it maximizes gas exchange of O₂ and CO₂ (Qureshi, 2008).

2.4.2 Particle deposition in the respiratory tract

Particle deposition in the respiratory tract depends on the amount of contaminated air inhaled, the size and density of the particle inhaled and the physical dimension of the respiratory tract (Salma *et al.*, 2002; Carvalho *et al.*, 2010). Deposition of particles mainly occurs through the following mechanisms (Witchi & Last, 2003; Yang *et al.*, 2008; Carvalho *et al.*, 2010):

2.4.2.1 *Inertial impaction:*

Inertial impaction occurs when airborne particulates generate enough momentum to keep its trajectory despite of air stream changes, as a result colliding with the walls of the respiratory

tract. An increase particle density and particle travel distance will enhance the chance of impaction.

2.4.2.2 **Sedimentation:**

This mechanism is a time-dependent process in which a particle settles due the influence of gravity. Because it is time-dependent, breath-holding may increase lung deposition due to the fact that more time is allowed for the particle to settle. With an increase of particle density and time spent in the airway, increased chances for sedimentation occurs.

2.4.2.3 **Diffusion:**

Diffusion occurs when particles are sufficiently small enough to undergo a random motion due to molecular bombardment. Brownian diffusion occurs mostly in areas where there is low bulk flow like the alveoli and bronchioles of the lungs.

All of these mechanisms for particle deposition are inversely related to particle size (Carvalho *et al.*, 2010).

In occupational settings, three aerodynamic fractions are discriminated, which play a deterministic role in the deposition and absorption of airborne particles. The three aerodynamic fractions are: 1) Inhalable fraction, particles with an aerodynamic diameter of up to 100 μm where it can be deposited in the nose and mouth during breathing. Particles accumulate in the mucus and can be sneezed or coughed out. It can also be swallowed making it possible for absorption through ingestion. This fraction has a 50% cut-point of 100 μm . 2) Thoracic fraction is particles with an aerodynamic diameter of less than 30 μm where it can be deposited in the lung airways. This fraction has a 50% cut-point of 10 μm . 3) Respirable fraction has a 50% cut-point of 4 μm and can be deposited in the gas exchange region (alveoli) (Belle & Stanton, 2007; DEPA, 2008).

2.4.3 Clearance of particles (respiratory defences)

Clearance or removal of inhaled particles can be described in two processes namely, mechanical clearance and absorptive process. For each area in the respiratory tract different clearance mechanisms are presented.

2.4.3.1 Upper respiratory or nasal clearance:

The nasal area lined with mucus serves as an initial filtering area for inhaled particulate matter via the mouth or nose. Particulates can be cleared by wiping or blowing when captured in the front portion of the nasal passages. Swallowing of inhaled particulates can also occur due to some of the particles captured on the mucociliary epithelium and transported down where it can be digested (Radiation Resources, 2009).

2.4.3.2 Tracheobronchial clearance:

The mucociliary escalator is the main clearance mechanism in this area. Other clearance mechanisms include phagocytosis for already deposited particles in this region (Radiation Resources, 2009).

2.4.3.3 Pulmonary clearance:

The mucociliary escalator plays a prominent role in the clearance of particles in this area. Particles can be cleared in an upward motion towards the tracheobronchial area where it can be removed by swallowing. Alveolar macrophages can also phagocytise particles, which then can be removed by lymphatic drainage (Whitshi & Last, 2003; Radiation Resources, 2009).

2.4.4 Respiratory exposure studies

Although published data on inhalable nickel exposure from previous studies in nickel production and primary user industries are available (Werner *et al.*, 1999), data specific in relation to respiratory exposure to nickel in refineries are limited. Debates on whether the 37 mm open face cassettes or the Institute of Occupational Medicine (IOM) sampler should be used have been futile. Nonetheless, it has become widely regarded that the IOM sampler is an acceptable reference sampler for sampling the inhalable fraction (Sivulka *et al.*, 2007). Hughson *et al.* (2010) reported on inhalable nickel exposure at nickel refineries and primary user industries using the IOM inhalable dust sampler. Results show that workers involved with the packing of solid nickel metal products were mostly exposed to metallic nickel and oxidic nickel species. Workers at the packaging area of nickel metal products had a geometric mean exposure of 0.08 mg m⁻³ (0.01 - 0.34 mg m⁻³), whilst workers packing nickel compounds had exposure results of 0.02 mg m⁻³ (0.01 - 0.10 mg m⁻³).

Aside from respiratory exposure, nickel deposition of airborne nickel can come in contact with the skin, and can lead to dermal exposure.

2.5 Dermal exposure

The skin is the most prominent organ of the human body, and is a key protective barrier between the external and the internal environment (Proksch *et al.*, 2008; Rawlings *et al.*, 2008). Permeation of nickel through intact skin is very low but increases through impaired or damaged skin (Larese Filon *et al.*, 2009).

Dermal exposure to substances can be assessed by using various methods. These methods can be grouped into three categories, namely (i) surrogate skin methods (interception methods), (ii) removal methods and (iii) fluorescent tracer methods (Cherrie *et al.*, 2000; ECS, 2006). The removal of substance methods, remove the substance, like for instance nickel from the skin surface can be done through skin wiping (Hughson *et al.*, 2010), tape stripping (Kristiansen *et al.*, 2000) and skin washing methods (Staton *et al.*, 2006).

A few studies reported on dermal exposure to nickel using skin wipes as a removal method. According to Du Plessis (2010), no golden standard regarding the assessment of dermal exposure currently exists. Liden *et al.* (2008) and Julander *et al.* (2010) used a paper-pak wetted with 0.5 ml of 1% of HNO₃. The skin was cleaned prior to the shift by washing and wiping. The areas were wiped 3 times with 3 wipes over the area at the end of the completed task. Hughson *et al.* (2010) used Jeyes "sticky finger" wet ones and assumed the workers' skin was uncontaminated before a shift and only collected prior to two breaks and at the end of the shift. Day *et al.* (2009) on the other hand used a Wash and Dry[®] wipe and collected samples prior to the shift and at lunch time. Du Plessis *et al.* (2010) reported dermal exposure at a refinery for workers responsible at the electro-winning area, the same as Hughson *et al.* (2010). The author used Ghostwipes[™] to collect the samples before and at the end of the shift on the exposed areas. The index finger and palm of the hand were collected prior to each of their two breaks. The results of the packaging area of nickel metal, nickel compounds and nickel powder of Hughson *et al.* (2010) are directly relevant to this study. The results obtained in these areas showed that nickel powder caused the highest overall dermal exposure, with the hand and forearms having a geometric mean exposure of 8.73 µg cm⁻², for the face, 15.16 µg cm⁻² was reported and the neck 6.20 µg cm⁻². For nickel metal products, hands and forearms total nickel exposure was measured to have a geometric mean of 1.17 µg cm⁻². For the face, total nickel exposure was 2.99 µg cm⁻². The packaging of nickel compounds yielded a geometric mean exposure of 1.17 µg cm⁻² for the hands and forearms and 0.73 µg cm⁻² for the face respectively.

In order to elucidate the protective properties of the skin and parameters influencing permeation of exogenous and endogenous substances via this barrier, a discussion will follow depicting skin histology, functions of the skin, skin barrier function and other factors influencing skin barrier function.

2.5.1.1 Histology of the skin

The skin is not merely the outer layer covering the body, but the biggest and one of the most important organs (Agache, 2004a; Darlenski *et al.*, 2009). It makes up 16% of an average bodyweight and covers a surface area of 1.8 m² (Agache, 2004a). It varies in thickness and differs according to the anatomical site and age of the individual. Microscopic appearance of aged skin shows a thinner epidermis than that of young skin (Waller & Maibach, 2005). Consequently the aged skin becomes less resistant to shearing forces and is easily torn after trauma (Chung *et al.*, 2002; Gambichler *et al.*, 2006). The skin is thicker on the feet and palms than the rest of the body (Agache, 2004a).

The skin has three different layers: the outer layer known as the stratum corneum (SC), the viable epidermis and the dermis. The skin is a dynamic organ and is in a constant state of change; dead cells on the stratum corneum are continuously shed and replaced by the inner cells moving up towards the surface. (Agache, 2004a; Darlenski *et al.*, 2009).

The stratum corneum serves as the physical and chemical barrier between the interior body and exterior environment (Proksch *et al.*, 2008; Rawlings *et al.*, 2008). The dermis is the deeper layer providing more structural support to the skin.

The SC consists of corneocytes, embedded in a lipid bilayer matrix and a cornified envelope. These corneocytes provide the actual physical barrier of the skin (Menon *et al.*, 2012) This forms a dense and compact structure often described as a “brick and mortar” structure (Darlenski *et al.*, 2009; Kezic & Nielsen, 2009), although, a more complete description of the SC includes corneodesmosomes (specialized desmosomes), that provide cohesion by binding homeophilically with proteins on adjacent cells (Rawlings *et al.*, 2008). These corneodesmosomes undergo gradual degradation so that they enable the continuous desquamation of the outermost corneocytes (Menon *et al.*, 2012).

The epidermis comprises of mainly keratinocytes, which synthesise a large amount of the protein called keratin. Protein bridges called desmosomes connect the keratinocytes, which are

in a constant state of transition from the deeper layers to the superficial layers. Keratin is a particularly tough protein that also forms a major part of hair and nails. It normally contains 20% water which helps to keep the skin soft, smooth and supple. The epidermis varies in thickness, from 0.05 mm on the eyelids to 1.5 mm on the feet and palms of the hands with an average thickness of 1.2 mm. (Agache, 2004a).

2.5.1.2 Functions of the skin

According to Foulds (2005), the skin is a metabolic organ giving rise to the protection and maintenance of homeostasis of the human body (Darlenski *et al.*, 2012). General functions of the skin are summarized by Agache (2004a), Bikle, (2011) and McGrath & Lai-Cheong, (2009) and include the following:

- The reduction of the harmful effects of ultraviolet rays (UV-rays) through the production of a pigment melanin.
- Providing mechanical protection and keeping the body's external shape.
- Providing chemical protection against foreign chemical substances.
- It helps with the prevention of water loss and endogenous fluid loss.
- The skin is self maintainable and self repairing, although the latter is not situated in the skin itself.
- Protection against environmental micro organisms through the up keeping of the "acid mantle".
- Acts as a sensory organ through tactile organs and informing the brain of the changes in the immediate environment.
- Aids with the regulation of body temperature.

2.5.1.3 Skin barrier function

The SC gives rise to the main physical barrier function (Proksch *et al.*, 2008; Kezic & Nielsen, 2009). The intact skin prevents exogenous substances from invading the body and fends off physical and chemical assaults (Agache, 2004a; Proksch *et al.*, 2008; Menon *et al.*, 2012). This characteristic of the skin can be seen as an outside – inside function, as it prevents xenobiotics from entering the body. It also has an inside - outside function that prevents uncontrolled loss of proteins, water and plasma components (Agache, 2004a; Proksch *et al.*, 2008).

The SC is the rate-limiting unit for penetration of substances across the skin (Darlenski *et al.*, 2009; Kezic & Nielsen, 2009). The lipid bilayer prevents uncontrolled water loss from the epidermis and regulates electrolyte movement across the SC (Darlenski *et al.*, 2009). The lipids are a complex mixture of ceramides, cholesterol, free fatty acids and some minor lipids. Unlike other biological membranes, it contains no phospholipids (Darlenski *et al.*, 2009; Hadgraft & Lane, 2009).

Permeability varies depending on the anatomical site being investigated. Anatomical sites with relatively high permeability are associated with smaller corneocyte sizes (Machado *et al.*, 2010). There is a direct relationship between path length of permeation and skin permeability as assessed by transepidermal water loss (TEWL) measurements (Hadgraft & Lane, 2009). The diffusion barrier results from both the properties of the lipids and the path length for diffusion. The latter depends on the number and layer of corneocytes and their size and cohesion. The major source of permeation is around the corneocytes, therefore, larger corneocytes will extend the route of permeation. Corneocyte sizes differ between anatomic sites, for example, facial skin is thinner, and has smaller corneocytes than arm skin, and this can directly be related to permeability. This leads to a smaller distance for xenobiotics to penetrate the skin and easier for TEWL to occur (Hadgraft & Lane, 2009). Agache (2004a) states that the three main and most important parameters that can most accurately determine, with the help of specialized equipment, the state of the skin's barrier function are, skin hydration, skin surface pH and TEWL.

2.5.1.4 Parameters and other factors influencing skin barrier function

2.5.1.4.1 Transepidermal Water Loss

TEWL is the term used to describe the amount of water that passes from the internal body through the SC of skin to the external body surface and surrounding areas when there is no sweat gland activity (Mündlein *et al.*, 2008; Kezic & Nielsen, 2009). TEWL is, therefore, used for studying the water barrier function of the human skin (Mündlein *et al.*, 2008). It is well known, the better the condition of the skin's protective layer, the water content is improved and the TEWL is lowered. Thus, an inverse relationship between TEWL and skin hydration can exist (Proksch *et al.*, 2008). Healthy skin has a low TEWL, thus increases in TEWL indicate a decreased skin barrier function (Rippke *et al.*, 2004; Mündlein *et al.*, 2008). TEWL measurement is a very effective way of discovering abnormalities in the protective layers of the skin, even before the consequences of these abnormalities become visible. The amount of water loss that

takes place in normal skin is very low but in atopic or damaged skin, the water loss will be much higher (Ramalho *et al.*, 2007; Mündlein *et al.*, 2008).

There are numerous instruments available on the market to measure TEWL. Two distinct methods of measuring TEWL are currently on the market namely, (1) open-chamber and (2) closed-chamber instruments. Open-chambers are open to the atmosphere surrounding the instrument and are easily influenced by air movement like turbulence and convection. Closed-chamber method on the other hand is enclosed from the atmosphere surrounding the instrument and is thus not influenced by air movement (Du Plessis *et al.*, 2013).

2.5.1.4.2 Skin hydration

Skin hydration is the capacity of the SC, which is composed of corneocytes and enriched with water-soluble natural moisturizing factor, to retain water (Sotodian & Maibach, 2012). According to Kezic & Nielsen (2009), hydration of the skin is a mechanism which can hinder/change the skin barrier function. When the stratum corneum fails to retain water it induces redness, dryness and impairs skin barrier function (Darlenski *et al.*, 2012). When the skin has been drenched in water for a long period of time or when evaporation is decreased, for example by the wearing of personal protective clothing (PPE) like a glove, increased skin hydration can occur and deterioration of the barrier can occur (Kezic & Nielsen, 2009). Electrical properties of the skin are dependent on the water content of the SC (Pirrot & Falson, 2004; Gabard *et al.*, 2006). Consequently resistance and capacitance contribute to the total impedance to an alternating resistance applied on the skin's surface (Du Plessis *et al.*, 2013). Therefore, skin hydration is measured as the electrical conductance or capacitance (Gabard *et al.*, 2006).

Numerous commercial skin hydration measurement instruments based on the above mentioned principles are available. Manufactured by Courage and Kazaka Electronic GmbH (2008), the Corneometer[®] is such an instrument that converts the total capacitance or conductance of the skin surface to arbitrary units (a.u.) of skin hydration.

2.5.1.4.3 Skin surface pH

The pH of the skin is, as defined by Agache (2004c), the negative logarithm of the concentration of the free hydrogen ions in a solution. Three main closely interconnected concepts may be considered in relation to skin surface pH: the “acid mantle”, the natural moisturizing factor (NMF) and the buffering capacity of the skin (Parra & Paye, 2003). The skin pH also plays a

significant role in the skin barrier homeostasis, the renovation of disrupted skin barrier and gives rise to the “acidic mantle” (Rippke *et al.*, 2002; Darlenski *et al.*, 2012). This mantle of the skin serves as a defence mechanism against pathogenic onslaughts (Rippke *et al.*, 2004; Schmid-Wendtner & Korting, 2006; Darlenski *et al.*, 2012). Not only does the natural moisturizing factor (NMF) help in maintaining the water retention capacity of the skin, but also have a relevant buffering capacity for the water in the corneocytes. The maintenance of the stratum corneum physiological acidity and elasticity of the skin may be facilitated by the buffering capacity (Chikakane & Takahashi, 1995; Parra & Paye, 2003). Ionisation of compounds in the stratum corneum is probably influenced by the acidic pH of the skin surface, however, the buffering capacity of the stratum corneum may enhance this process and regulate the stratum corneum pH gradient (Warner *et al.*, 1995, Parra & Paye, 2003).

According to Agache (2004c), the skin surface pH ranges between 4.2 and 6.1 and is dependent on the site or anatomical area. Measuring the skin surface pH can be done with four glass planar electrode instruments that are commercially available and that are in line with the universal method (Parra & Paye, 2003; Agache, 2004). One of the instruments used is the Skin-pH-Meter[®] that is manufactured by Courage and Kazaka Electronic GmbH (2008).

2.5.1.4.4 Other factors influencing skin barrier function

Skin surface pH, skin hydration and TEWL play an important role in determining skin barrier function. Endogenous, exogenous, and environmental-related factors need to be taken into account when assessing skin barrier function and the measurement thereof (Agache, 2004d; Tupker & Pinnagoda, 2006; Proksch *et al.*, 2008; Du Plessis & Eloff, 2010; Du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013). Some of these factors are summarized below in Table 3 that may affect the three parameters used to measure skin barrier function for this study. A brief description of individual factors affecting skin barrier function will follow.

2.5.1.4.4.1 Endogenous factors

In ageing, skin barrier function deteriorates. During the aging process, TEWL and skin hydration decreases (Barel & Clarys, 2006; Farinelli & Berardesca, 2006; Darlenski *et al.*, 2009), while skin surface pH increases as a person ages (Fluhr *et al.*, 2006; Marrakchi & Maibach, 2007; Man *et al.*, 2009). According to Marrakchi & Maibach, (2007) the age of the individual does not affect TEWL.

Controversial data exist on whether race is an influential factor in determining TEWL and stratum corneum hydration (Fluhr *et al.*, 2008; Rawlings *et al.*, 2008; Darlenski *et al.*, 2009; Darlenski *et al.*, 2012). There are, however, authors stating that ethnicity influences hydration (Warrier *et al.*, 1996), and others suggesting there is no influence (Berardesca *et al.*, 1991; Berardesca *et al.*, 1998). According to Darlenski *et al.* (2012), pH is influenced by race. Some studies have, however, found data that are controversial, suggesting that pH is not influenced or that there is not enough evidence to make conclusions (Warrier *et al.*, 1996; Berardesca *et al.*, 1998).

Many studies have found that distinct anatomical areas possess different morphological and functional characteristics and, therefore, influence TEWL, skin hydration and skin surface pH (Warrier *et al.*, 1996; Ehlers *et al.*, 2001; Barel & Clarys, 2006; Farinelli & Berardesca, 2006; Kim *et al.*, 2006 Marrakchi & Maibach, 2007; Darlenski *et al.*, 2009; Darlenski *et al.*, 2012; Kleesz *et al.*, 2012).

According to Proksch *et al.* (2008), TEWL and skin hydration is influenced by the health of one's skin (Tagami *et al.*, 2002). With atopic dermatitis, skin hydration values are respectively lower and TEWL values higher (Proksch *et al.*, 2008). Skin surface pH is also influenced by skin health (Schmid-Wendtner & Korting, 2006; Jungersted *et al.*, 2010).

2.5.1.4.4.2 Exogenous factors

In occupational settings, due to the nature of the work, physical and mechanical irritation and chemical onslaughts commonly occur that damage the skin and disrupt the skin barrier. Factors such as occlusion, skin damage, skin washing together with wet work and solvents can influence skin hydration (Zhai & Maibach, 2002; Voegeli, 2008; Kezic & Nielsen, 2009; Wetzky *et al.*, 2009). Wet work alone can increase skin hydration following lengthened or recurrent exposure (Kezic & Nielsen, 2009). According to Voegeli (2008), skin washing and wet work can influence TEWL and skin hydration. Although personal protective equipment is used as the last line of defense to reduce workers' exposure and to protect them from injuries, occlusion created by the wearing of protective gloves, prevents evaporation of water leading to an increase of water in intracellular spaces across the SC spectrum, swelling of corneocytes and thus influencing skin barrier function. Factors that have a definite influence in increasing TEWL are occlusion, damaged skin, skin washing and wet work (Korting *et al.*, 1991; Fluhr *et al.*, 2006; Wetzky *et al.*, 2009; Jungersted *et al.*, 2010). A study done by Ramsing and Agner (1996) showed that glove occlusion dramatically decreases skin barrier function, as measured by

TEWL. The authors also concluded that gloves may be a detrimental factor in the pathogenesis of irritant contact dermatitis. Skin surface pH is also influenced by exogenous factors like occlusion, skin washing and wet work (Hartmann, 1983; Korting *et al.*, 1991; Moldovan & Nanu, 2010). Whilst washing of the hands, different soaps often increase or decrease skin surface pH according to whether the soap is alkaline or acidic base (Moldovan & Nanu, 2010).

2.5.1.4.4.3 Environmental and measurement factors

Darlenski *et al.* (2009) and Tupker and Pinnagoda, (2006) found that environmental factors such as air movement, ambient temperature, relative humidity, direct sunlight and seasonal changes influence TEWL readings. Darlenski *et al.* (2009) also found that skin hydration is influenced by air movement, ambient temperature and relative humidity, but controversial data exist on whether seasons influence skin hydration. Qiu *et al.* (2011) found that seasons do influence skin hydration. The question on whether relative humidity can change skin hydration was also concluded in a study done by Barel and Clarys, (2006). A study done by Abe *et al.* (1980) found that skin surface pH and TEWL is influenced by season changes. No conclusion can be made to prove that skin surface pH is influenced by air movement, ambient temperature, relative humidity or direct sunlight.

Table 3. Endogenous, exogenous, and environmental factors affecting skin surface pH, TEWL and skin hydration (Combined from; Du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013).

	TEWL		Skin hydration		Skin surface pH	
	Influence	Ref.	Influence	Ref.	Influence	Ref.
<u>Exogenous factors</u>						
Occlusion	Yes	(Wetzky <i>et al.</i> , 2009) (Jungersted <i>et al.</i> , 2010) (Ramsing & Agner, 1996)	Yes	(Kezic & Nielsen, 2009) (Zhai & Maibach, 2002)	Yes	(Hartmann, 1983)
Skin washing and wet work	Yes	(Voegeli, 2008) (Korting <i>et al.</i> , 1991)	Yes	(Kezic & Nielsen, 2009) (Voegeli, 2008)	Yes	(Moldovan & Nanu, 2010) (Korting <i>et al.</i> , 1991)
Skin damage	Yes	(Fluhr <i>et al.</i> , 2006)	Yes	(Wetzky <i>et al.</i> , 2009) (Kezic & Nielsen, 2009)	-	
<u>Endogenous factors</u>						
Age	Yes	(Darlenski <i>et al.</i> , 2009) (Farinelli & Berardesca, 2006)	Yes	(Darlenski <i>et al.</i> , 2009) (Farinelli & Berardesca, 2006)	Yes	(Fluhr <i>et al.</i> , 2006) (Marrakchi & Maibach, 2007)
	No	(Marrakchi & Maibach, 2007)		(Barel & Clarys, 2006)		(Man <i>et al.</i> , 2009)

Table 3: (Continued)

	TEWL		Skin hydration		Skin surface pH	
	Influence	Ref.	Influence	Ref.	Influence	Ref.
Ethnicity	Controversial	(Darlenski <i>et al.</i> , 2009)	Controversial	(Darlenski <i>et al.</i> , 2009)	Yes	(Darlenski <i>et al.</i> , 2012)
		(Darlenski <i>et al.</i> , 2012)		(Darlenski <i>et al.</i> , 2012)	Controversial	(Warrier <i>et al.</i> , 1996)
	Yes	(Warrier <i>et al.</i> , 1996)		(Fluhr <i>et al.</i> , 2008)	No	(Berardesca <i>et al.</i> , 1998)
	No	(Berardesca <i>et al.</i> , 1991) (Berardesca <i>et al.</i> , 1998)		(Rawlings <i>et al.</i> , 2008)		
Anatomical position	Yes	(Darlenski <i>et al.</i> , 2009)	Yes	(Darlenski <i>et al.</i> , 2009)	Yes	(Darlenski <i>et al.</i> , 2012)
		(Darlenski <i>et al.</i> , 2012)		(Darlenski <i>et al.</i> , 2012)		(Ehlers <i>et al.</i> , 2001)
		(Marrakchi & Maibach, 2007)		(Barel & Clarys, 2006)		(Kim <i>et al.</i> , 2006)
		(Warrier <i>et al.</i> , 1996)		(Farinelli & Berardesca, 2006)		(Marrakchi & Maibach, 2007)
		(Kleesz <i>et al.</i> , 2012)		(Kleesz <i>et al.</i> , 2012)		(Kleesz <i>et al.</i> , 2012)
Skin health	Yes	(Proksch <i>et al.</i> 2008)	Yes	(Proksch <i>et al.</i> 2008)	Yes	(Schmid-Wendtner & Korting, 2006)
		(Tagami <i>et al.</i> , 2002)				(Jungersted <i>et al.</i> , 2010)

Table 3: (Continued)

	TEWL		Skin hydration		Skin surface pH	
	Influence	Ref.	Influence	Ref.	Influence	Ref.
<u>Environmental and measurement factors</u>						
Season	Yes	(Darlenski <i>et al.</i> , 2009) (Tupker & Pinnagoda, 2006) (Abe <i>et al.</i> 1980)	Yes	(Qiu <i>et al.</i> 2011) Controversial (Darlenski <i>et al.</i> , 2009)	Yes	(Abe <i>et al.</i> 1980)
Air movement	Yes	(Darlenski <i>et al.</i> , 2009) (Tupker & Pinnagoda, 2006)	Yes	(Darlenski <i>et al.</i> , 2009)	-	
Ambient temperature	Yes	(Darlenski <i>et al.</i> , 2009) (Tupker & Pinnagoda, 2006)	Yes	(Darlenski <i>et al.</i> , 2009)	-	
Relative humidity	Yes	(Darlenski <i>et al.</i> , 2009) (Tupker & Pinnagoda, 2006)	Yes	(Darlenski <i>et al.</i> , 2009) (Barel & Clarys, 2006)	-	
Direct light	Yes	(Darlenski <i>et al.</i> , 2009) (Tupker & Pinnagoda, 2006)	-		-	

-, No data.

2.6 Human health effects of Nickel

The most common adverse health effect due to occupational exposure to nickel and its compounds is skin allergies. More severe adverse health effects are lung fibrosis and lung cancer, as metallic nickel is considered as a possible human carcinogen (Oller, 2002; IARC, 2012).

2.6.1 Allergic contact dermatitis

In occupational and general settings it is well known that contact with metals especially nickel can be responsible for allergic contact dermatitis (Larese *et al.*, 2007). The risk of allergic contact dermatitis exists in humans if there is sufficient dermal exposure to nickel ions (Hughson *et al.*, 2010).

Allergic contact dermatitis is a cell mediated delayed type IV hypersensitivity reaction in the skin (Vahter *et al.*, 2007; Gober & Caspari, 2008). As a result of xenobiotics penetrating into the skin, it occurs after chemically reacting with self proteins, and eventually resulting in hapten-specific immune response (Gober & Caspari, 2008). There are two distinct phases of allergic contact dermatitis namely a sensitization or induction phase where the host is immunized to the allergen and the elicitation phase, characterized by a rapid secondary immune response after re-exposure to the allergen such in this case nickel (Alenius *et al.*, 2008; DEPA, 2008; Thyssen & Menne, 2010). Allergic contact dermatitis is evident in the elicitation phase (Alenius *et al.*, 2008).

Allergic contact dermatitis is an inflammatory response that is dependent on antibodies. The secretion of cytokines by helper T cells is activated by the antigen in that specific area (Saint-Mezard *et al.*, 2004; DEPA, 2008). These cytokines themselves act as inflammatory mediators and activate macrophages to secrete their mediators (DEPA, 2008).

No cure for contact dermatitis exists, but treatment for this chronic and life-long condition is symptomatic through the use of anti-inflammatory corticosteroids. A control measure for this disease is avoidance that seems to be the only means of prevention (DEPA, 2008).

2.6.2 Respiratory effects

The Danish Environmental Protection Agency (DEPA) 2008 considers nickel to be a potential respiratory sensitizer, due to asthma diagnoses in exposure to nickel sulphate and metallic nickel, but no threshold for sensitization currently exists.

2.6.3 Carcinogenesis

Metallic nickel is classified by the International Agency for Research on Cancer (IARC) as a possible carcinogenic to humans (group 2B) (IARC, 1990). All nickel compounds are considered carcinogenic to humans (group 1) (DEPA, 2008; IARC, 2012). Severe adverse health effects include lung fibrosis, lung and nasal cancer (Oller, 2002).

Direct mechanisms for nickel-induced carcinogenesis are not clear and have been the subject of numerous experimental and epidemiologic studies. The proposed mechanism involves genetic and epigenetic routes (Zhao *et al.*, 2009; Lee *et al.*, 2012). Beyersmann and Hartwig's (2008) study proposed three indirect mechanisms for nickel's availability to (i) induce the formation of reactive oxygen species and aggravation of genotoxicity (Zhao *et al.*, 2009), (ii) interfere with DNA repair processes and lastly (iii) to induce enhanced cell proliferation (Xu *et al.*, 2011).

Evidence given suggests that nickel and nickel compounds have a vast effect on one's health. Therefore, it is clear that not only can respiratory monitoring take place but it needs to be in conjunction with dermal monitoring, to reduce and control exposure at the work place.

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CHAPTER 3

ARTICLE

This article will be submitted to the Annals of Occupational Hygiene. The author's instructions are as follows:

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Dermal and respiratory exposure to nickel in a packaging section of a base metal refinery

HENDRIK J CLAASSENS, FREDERIK C ELOFF, JOHANNES L DU PLESSIS

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

Corresponding Author

Prof J.L du Plessis

School of Physiology, Faculty of Health Sciences, North-West University, Potchefstroom Campus

Private Bag X6001

Potchefstroom

2520

South Africa

Tel: +27 018 299 2434; Fax: +27 018 299 2433

E-mail: Johan.DuPlessis@nwu.ac.za

Word count: 5724

Abstract:

Objectives: The objectives of this study were to assess dermal and respiratory exposure of workers exposed to nickel in a packaging section at a South African base metal refinery and to assess the change in skin barrier function during a work shift by measuring percentage change in trans epidermal water loss (TEWL), skin hydration and skin surface pH. Skin health was established with a skin questionnaire. Surfaces that workers may come into contact with were also assessed.

Method: Respiratory and dermal exposure assessment was done concurrently. Respiratory exposure was assessed and analysed by using the National Institute for Occupational Safety and Health (NIOSH) method 7300. The Institute of Occupational Medicine (IOM) inhalable aerosol sampler was used for personal air sampling. The TEWL index, skin hydration and skin surface pH of the index finger, palm, forearm and forehead were measured before and at the end of the shift with a Derma Measurement Unit, EDS 12 and Skin-pH-Meter[®] pH 905. These measurements were reported as percentage change in skin barrier function during the shift. Dermal exposure samples were collected with Ghostwipes[™] from the index finger and palm of the dominant hand before, during and at the end of the shift, while samples from the forearm and forehead were only collected before and after the shift. Surface sampling was collected and all wipes were analysed for nickel according to the NIOSH method 9102, using inductively coupled plasma-atomic emission spectrometry.

Results: Respiratory exposure for the whole group of workers in a packaging section was well below the eight hour Time Weighted Average (TWA) respiratory Occupational Exposure Limit (OEL) of 0.5 mg m^{-3} for nickel. Dermal nickel loading was detected for all the job categories on all the anatomical areas even before the shift had commenced. During the shift more nickel was detected on the index finger and palm of the hand. Levels on the forearm and forehead were much lower in comparison with the index finger and the palm of the hand. Workplace surfaces, which workers may come into contact with on a daily basis, were also contaminated with nickel. Forklift drivers showed high exposure on the index finger and palm of their hands, and this can be attributed to them not wearing any gloves for hand protection. An increase in percentage change for TEWL was seen for most of the job categories on all anatomical areas measured during the shift. Percentage change in skin surface pH and skin hydration varied among job categories during the shift.

Conclusion:

Respirable exposure to nickel was below the OEL. Dermal exposure was evident on all anatomical areas for all job categories before the shift had commenced. Personal protective equipment was provided to all employees, but forklift drivers did not wear gloves when operating the forklift. Changes in TEWL and to a lesser extent skin hydration, suggest a deterioration in skin barrier function during the shift. Forklift drivers as well as plate washers may be the highest risk job categories in developing allergic contact dermatitis. Several measures to lower respiratory and dermal exposure to nickel are also recommended.

Keywords:

Respirable, skin exposure, skin hydration, TEWL, skin surface pH, skin barrier function, hazardous chemicals.

Introduction

Exposure to nickel and nickel compounds may be extremely detrimental to human health as all nickel compounds are considered carcinogenic to humans (group 1). This includes cancers of the lung, nasal cavity and paranasal sinuses (IARC 2012). Metallic nickel is classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen to humans (group 2B) (IARC, 1990). The IARC Monographs volume 100C reported elevated risk of lung and nasal cancers of workers involved in a variety of nickel refining and ore smelting processes, which included high-temperature processing of nickel matte, nickel-copper matte and electrolytic refining (IARC, 2012).

The respiratory tract has traditionally been seen as the main route of exposure through inhalation and was considered to be the most important route of exposure (Semple, 2004). Subsequently the main focus of occupational hygiene is respiratory exposure to chemical stressors. With this said, the potential health effects following skin exposure cannot be ignored.

Aside from nickel's strong carcinogenic properties via respiratory exposure, it is also the most common contact allergen in the general population. Nickel also causes type IV delayed hypersensitivity reactions in occupational settings. Generally sensitisation occurs after prolonged exposure of direct skin contact with nickel ions (Vahter *et al.*, 2007).

One of the most important functions of the skin is to provide a physical barrier (Proksch *et al.*, 2008; Kezic & Nielsen, 2009) by preventing exogenic substances from invading the body and fending off physical and chemical assaults. The structure of the stratum corneum varies significantly between anatomical positions and consequently these differences play an important role in the permeability of the skin (Agache, 2004a). The *in vitro* rate of permeation for nickel through intact or healthy skin is considered by Hostynek (2003) to be very low, but yet it elicits allergic skin reactions following contact in individuals that are sensitised.

One of the main findings from Du Plessis *et al.* (2010) when assessing skin barrier function is how workers perceive their own skin condition. Workers are often under the impression that they have a healthy skin, while skin hydration levels and trans epidermal water loss (TEWL) indicate the opposite. Agache (2004b) states that the three leading

and most important parameters that can most accurately determine the state of the skin's barrier function are, skin hydration, skin surface pH and TEWL.

TEWL is the term used to describe the amount of water that passes from the internal body through the stratum corneum of skin to the external body surface when there is no sweat gland activity (Mündlein *et al.*, 2008).). Three main closely interconnected concepts may be considered in relation to skin surface pH: the "acid mantle", the natural moisturizing factor (NMF) and the buffering capacity of the skin (Parra & Paye, 2003). The pH of the skin also plays a significant role in the skin barrier homeostasis and gives rise to the "acidic mantle" (Rippke *et al.*, 2002). Not only does the natural moisturising factor (NMF) help in maintaining the water retention capacity of the skin, but also have a relevant buffering capacity for the water in the corneocytes. The maintenance of the stratum corneums physiological acidity and elasticity of the skin may be facilitated by the buffering capacity (Chikakane & Takahashi, 1995; Parra & Paye, 2003). Ionisation of compounds in the stratum corneum is probably influenced by the acidic pH of the skin surface, however, the buffering capacity of the stratum corneum may enhance this process and regulate the stratum corneum pH gradient (Warner *et al.*, 1995, Parra & Paye, 2003). It is well known that compromised skin is linked with an increase in TEWL, which is an indication of impaired skin barrier function (Mündlein *et al.*, 2008) and is frequently correlated with low hydration of the stratum corneum (Proksch *et al.*, 2008). Sweating from physical, thermal and emotional mechanisms increases skin hydration and TEWL values (Pinnagoda *et al.*, 1989; Goh, 2006; Du Plessis *et al.*, 2013), but can be controlled by allowing adequate acclimatization of the workers to the environment and performing measurements under controlled environmental conditions (Pinnagoda *et al.*, 1990; Berardesca, 1997; Rogiers, 2001; Du Plessis *et al.*, 2013).

Nickel is only one of many chemical stressors found at a base metal refinery to which workers may be exposed, the others include examples such as cobalt and sulphuric acid. Co-sensitisation of nickel together with cobalt may increase the risk of developing allergic contact dermatitis (Lidén and Wahlberg, 1994; Wahlberg and Lidén, 2000; Du Plessis *et al.*, 2013). A few studies reported dermal exposure to nickel using skin wipes as a removal method (Lidén *et al.*, 2008; Du Plessis *et al.*, 2010; Hughson *et al.*, 2010; Julander *et al.*, 2010). A study done by Hughson *et al.* (2010) reported dermal and inhalation exposure to nickel in nickel production and primary user industries. Du Plessis *et al.* (2010) reported dermal exposure to nickel and skin barrier function in an electro-

winning plant (tank house) of a base metal refinery using wipes for dermal exposure and measured TEWL and skin hydration indices to indicate skin barrier function.

Dermal exposure to nickel at refineries and primary user industries were only published three years ago (Hughson *et al.*, 2010; Du Plessis *et al.*, 2010). This study on respiratory and dermal exposure of refinery workers aims to evaluate the respiratory and dermal exposure. The percentage change in skin parameters (TEWL, skin hydration and skin surface pH) during a work shift will be assessed in accordance to international guidelines (Du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013). In addition to this, surface sampling to surfaces that workers may come into contact with on a daily basis will be sampled and a skin questionnaire will be filled out by the workers.

Methodology

Workers participating in this study were processors (n = 19) working in the packaging area with different job descriptions. The job descriptions included: (1) Nickel plate washers, (2) Nickel sheet strappers, (3) Nickel cutting operators, (4), Forklift drivers and (5) Weighbridge operators. The average age of the workers was 44 years. The workers wore an acid repellent olive green two-piece overall and a disposable FFP2 (Filtering Face piece, class P2) face mask for respiratory protection when house cleaning was done. The nickel sheets that were handled often had razor sharp edges, and due to the risks of cuts, two types of gloves were worn simultaneously, namely a cotton liner glove and a silver talon whizard[®] glove. The last mentioned was replaced once it was damaged based on the opinion of the worker himself.

This study was performed during the summer and ambient temperatures under which skin measurements were measured ranged from 21 °C to 23 °C, while relative humidity ranged between 40% and 43%.

Work place description

A nickel sulphate solution is pumped to an electro-winning plant (tank house) where metallic nickel is recovered using an electrolytic process. Nickel sheets/cathodes are removed from the cells after approximately seven days. These cathodes/nickel sheets, with metallic nickel deposited on them are transported to an adjacent area for cutting, packing and transport. There are a few processes inside this area performed by different workers. Nickel sheets are washed by a washer and weighed upon entering the area by

a weighbridge operator. Samples are taken to establish the quality of nickel. The nickel sheets are either cut into small strips by a nickel cutter and packed into 250 kg drums or packed together and strapped by a nickel sheet strapper before being transported to their destination. All the sheets are transported in this area by a forklift driver. These activities occur in a single shift that starts at 7h00 until 15h00 from Monday through to Friday.

Respiratory exposure

Personal airborne nickel dust sampling was conducted by using the Institute of Occupational Medicine (IOM) inhalable aerosol sampler, 0.8 μm cellulose ester membrane filters and cellulose backup pads. Apex personal sampling pumps (Cassella[®], United Kingdom) and Gilair personal air samplers (Gilian[®], U.S.A), were calibrated at a flow rate of 2.0 l/min before and after use. The sampling head was attached in the breathing zone of each worker (collar of protective jacket) for the whole duration of the shift to assess eight hour exposure. Samples for nickel were analysed by a South African National Accreditation System (SANAS) accredited laboratory using the National Institute for Occupational Safety and Health method 7300 (NIOSH, 2009).

Dermal Sampling

A removal method was used to assess dermal exposure to nickel. Commercial skin wipes, Ghostwipes[™], that were separately wrapped and moisturised with deionised water by the manufacturer, were used to collect the samples from each worker, before the shift, prior to the tea break, prior to the lunch break and at the end of the shift. Samples were collected from the ventral side of the index finger and palm of the dominant hand before the shift, prior to the tea and lunch break and at the end of the shift. The index finger wipes were collected at the two most distal joints. By making a finger trace of the two most distal joints on paper the surface area was cut out and weighed. Together with the surface area a 4 cm^2 reference area was also cut out and calculated. The surface areas were repeatedly weighed ($n=3$) on a scientific Sartorius balance (Sartorius, model nr. BP211) to determine their average mass. The surface area of the two distal joints = mass of finger trace/mass of one cm^2 . Samples for the forearm and forehead were taken before the start of the shift and at the end of the shift. Acetate sheet templates (10 cm^2) were used to maintain a controlled and uniform area for each wipe. For every sample taken a new pair of vinyl disposable gloves were used by the

researcher collecting the samples. Each sample taken consisted of a single wipe that was wiped three times consecutively across the same exposed/sampling area. All samples taken were placed and transported in storage vials. Samples were taken to an accredited analytical laboratory and were analysed for nickel in accordance with NIOSH method 9102 using inductive coupled plasma-atomic emission spectrometry (NIOSH, 2009). The limit of detection for the analytical method is 0.0001 mg per sample. Results are given as $\mu\text{g cm}^{-2}$.

Surface sampling

Workers are most likely to come into contact with surfaces on a daily basis in the packaging area as well as the tea room. Uneven surfaces such as forklift steering wheels, hand knobs, door handles and strapping machines were wiped three times without using a template. Flat surfaces such as packaging drums, tea room tables and control room tables were wiped by using an acetate sheet template (100 cm^2), to represent an area. Each sample consisted of a Ghostwipe™, which was used to wipe the area in an s-pattern overlapping each other. Upon each wipe, the wipe was folded inward and repeated three times. The same storage and analysing methods were used as described in the dermal sampling method. Results were expressed as micrograms nickel per square centimetre ($\mu\text{g cm}^{-2}$), or micrograms nickel per sample (μg).

Percentage change in skin barrier function

TEWL and hydration indices of the skin were measured by using a Dermal Measurement Unit, EDS 12 (EnviroDerm, UK). Skin surface pH was measured by using a Skin-pH-Meter® pH 905 (Courage+Khazaka electronic, Germany). TEWL measurements were taken on the index finger, palm of the dominant hand and forehead at the beginning and end of the shift. Hydration indices and skin surface pH were measured on the index finger and palm of the dominant hand, forearm and forehead at the beginning of the shift (baseline measurement) and at the end of the shift. The effect that a workplace have on skin barrier function during a work shift can be measured through the changes in SH, TEWL and skin surface pH according to international guidelines (Du Plessis *et al.*, 2013, Stefaniak *et al.*, 2013), therefore results of this study are reported as the percentage change relative to the before the shift (baseline) measurement.

Skin condition questionnaire

Dalgard *et al.* (2003) developed a self-reported skin questionnaire that comprised of ten questions to quantify the absence or presence of skin diseases. This questionnaire was translated to Setswana, the native language of the workers. According to Dalgard *et al.* (2003), scores higher than 1.3 for non-health-care seeking populations have an increased risk of developing skin diseases.

Ethical aspects

Workers volunteered to take part as this study was scientific of nature. The privacy, integrity and dignity of all participants in this study were protected. All the participants were informed before the study commenced about the research's aim, method and potential results which can benefit their own health. The results from the research given to the participants' employer can be used for monitoring and implementing control measures to reduce participants' exposure to hazardous chemicals in the workplace. The Ethics Committee of the North-West University approved this assessment to conduct dermal exposure at a base metal refinery (number NWU-0026-07-S6). The respiratory exposure assessment was done as part of the continuous monitoring programme at the base metal refinery.

Statistical analysis

Due to the small number of workers in each job category and the data not being distributed normally, personal nickel exposure, dermal exposure and skin barrier function were analysed using the Kruskal-Wallis rank test, the non-parametric one-way analysis of variance (ANOVA). All pairwise comparisons were analysed by the Wilcoxon – pairwise comparison test and multiple comparison test (Tukeys, Bonferoni's and Scheffe's method). (Spotfire S+ Program version 8.1.1, TIBCO; 2008). All results with a p-value ≤ 0.05 were considered to be statistically significant.

Results

Respiratory exposure

The time weighted average (TWA) respiratory exposure data are shown in Table 1. The mean TWA respiratory exposure ranged between the nickel cutting operators (lowest) and the forklift drivers (highest) with an average of $0.04 \pm 0.03 \text{ mg m}^{-3}$ for the job

categories. The exposure of the total group was well below the 8 hour TWA respiratory Occupational Exposure Limit of 0.5 mg m⁻³ for nickel as stipulated in Table 2 of the Chapter 22 Schedules, promulgated under the Mine Health and Safety Act (MHSA, 29 of 1996). No job categories exposure exceeded the Threshold Limit Value (TLV) of 1.5 mg m⁻³ of the American Conference of Governmental Industrial Hygienist (ACGIH, 2013). Two exposures of the weighbridge operators were below the Recommended Exposure Limit (REL) of 0.015 mg m⁻³ as stipulated by NIOSH (NIOSH, 2009). The Workplace Exposure Limit (WEL) of 0.5 mg m⁻³ for nickel was also not exceeded (HSE, 2005). No statistical differences could be found between the different job categories.

Table 1. TWA respiratory nickel exposure (mg m⁻³) of processors in the nickel packaging area.

Job Categories	n	Mean	SD	Min	Max	P90	%≥1.5*	%≥0.5†	%≥0.015**
Forklift driver	4	0.06	0.04	0.03	0.10	0.10	0	0	100
Cutting operator	5	0.03	0.01	0.02	0.04	0.04	0	0	100
Sheet strapper	4	0.06	0.03	0.03	0.11	0.09	0	0	100
Plate washer	3	0.03	0.02	0.02	0.04	0.04	0	0	100
Weighbridge operator	8	0.03	0.03	0.01	0.09	0.06	0	0	75
Grouped	24	0.04	0.03	0.01	0.11	0.10	0	0	91.67%

n, number of measurements; mean; SD, standard deviation of mean ; P90, 90th percentile.

*% Measurements greater or equal to the Threshold Limit Value (ACGIH, 2013) of 1.5 mg m⁻³ for metallic nickel.

† Measurements greater or equal to the Time Weighed Average Occupational Exposure Limit (MHSA, Table 2 of Regulation 22) and the Workplace Exposure Limit (HSE, 2005) of 0.5 mg m⁻³ for metallic nickel.

** Measurements greater or equal to the Recommended Exposure Limit (NIOSH, 2009) of 0.015 mg m⁻³ for metallic nickel.

Dermal exposure

Dermal exposure to nickel for the index finger, palm, forearm and forehead is depicted in Figures 1A - D respectively. Workers had detectable levels of nickel before the shift commenced on all anatomical areas. Mean index finger exposures were variable, ranging from 1.34 to 5.08 $\mu\text{g cm}^{-2}$ for the forklift operators, 0.72 to 2.00 $\mu\text{g cm}^{-2}$ for the cutting operators, 1.02 to 1.89 $\mu\text{g cm}^{-2}$ for the sheet strappers, 1.89 to 6.74 $\mu\text{g cm}^{-2}$ for the plate washers, 1.11 to 2.09 $\mu\text{g cm}^{-2}$ for the weighbridge operators and 1.9 to 2.82 $\mu\text{g cm}^{-2}$ for the total group. For the forklift drivers index finger (Fig 1A), before shift exposure was significantly lower than that of break 1 and 2. Cutting operators before shift exposure was significantly lower than that of break 2. For the total group before shift exposure was significantly lower than that of break 1, 2 and at the end of the shift. Significant statistical differences existed between the forklift drivers and plate washers at break 1. Break 1 exposure results showed that the forklift drivers' exposure was significantly higher than that of cutting operators, sheet strappers and weighbridge operators, while plate washer's exposure was significantly higher than that of cutting operators, sheet strappers and weighbridge operators. At the end of the shift, forklift drivers exposure was significantly higher than that of the sheet strappers.

Figure 1B depicts exposure results of the palm. Before shift nickel exposure for the forklift drivers was significantly lower ($0.64 \pm 0.18 \mu\text{g cm}^{-2}$) than that of break 1 ($3.52 \pm 0.80 \mu\text{g cm}^{-2}$) and break 2 ($2.20 \pm 0.49 \mu\text{g cm}^{-2}$). Weighbridge operators before shift exposure results were significantly lower than the end of shift results. For the total group, before shift exposure was significantly lower than that of break 1, break 2 and the end of the shift. For the forklift drivers, break 1 nickel exposure was significantly higher than weighbridge operators' exposure.

For the forearm (Fig 1C), before shift exposure for the forklift drivers, weighbridge operators as well as the total group were significantly lower than that at the end of the shift. No statistical differences between nickel exposures for the different job categories were found for the forearm. Dermal nickel exposure for the forehead is depicted in Figure 1D. Before shift exposure was significantly lower than that of the end of the shift for sheet strappers, weighbridge operators and for the total group. At the end of the shift, forklift drivers' exposure ($1.77 \pm 0.51 \mu\text{g cm}^{-2}$) was significantly higher than that of the total group ($0.99 \pm 0.14 \mu\text{g cm}^{-2}$).

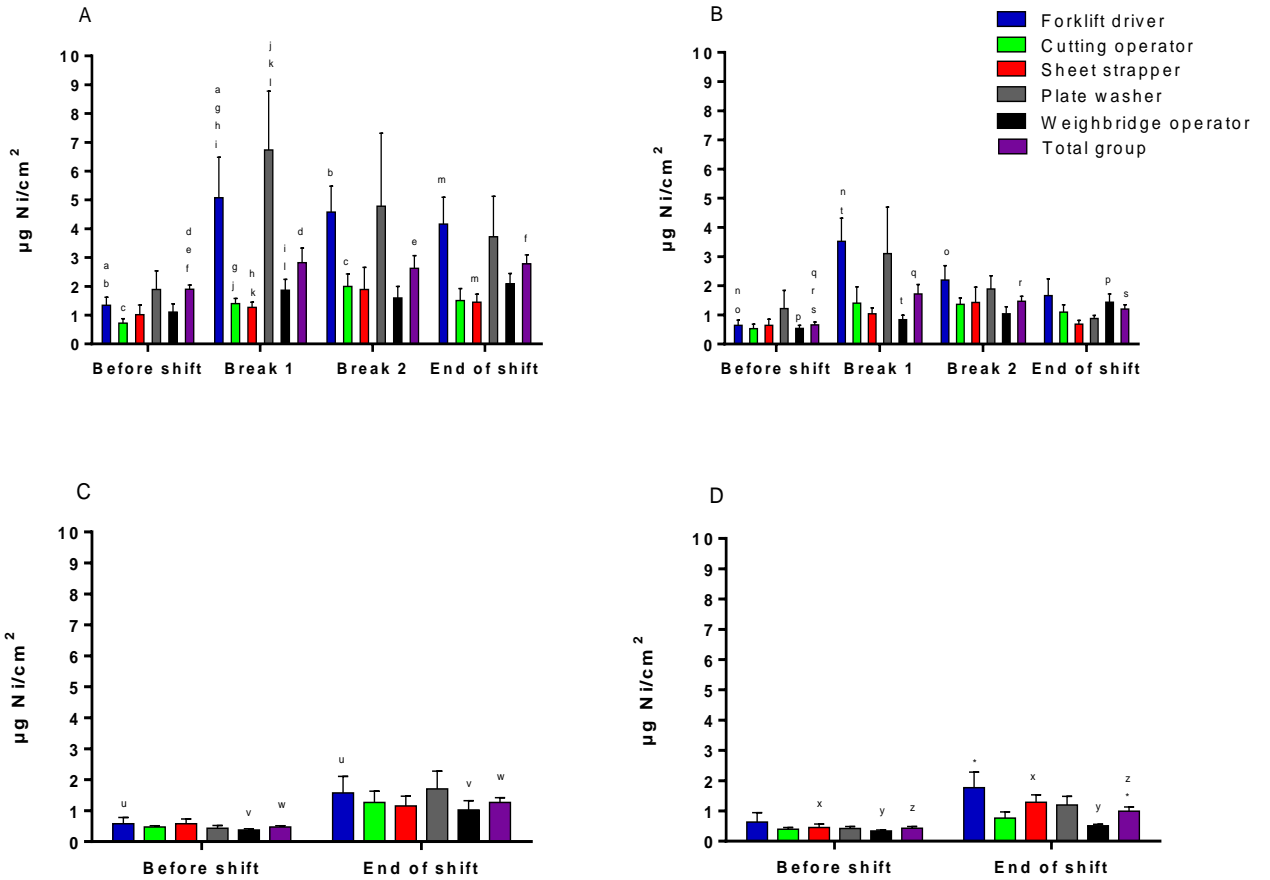


Figure 1. Full-shift dermal exposure to nickel for the (A) Index finger, (B) Palm, (C) Forearm and (D) Forehead (mean ± SD); Letters a-z and * indicates statistical significant differences ($p \leq 0.05$).

Surface exposure

Nickel was detected on surfaces such as door handles, forklift steering wheels and hand knobs, strapping machines and packaging drums, ablution door facilities and basins, which workers are more likely to come in contact with on a daily basis. The amount of nickel on these surfaces ranged between 0.264 µg to 0.709 µg. Nickel collected from flat surfaces in the tea room and control room ranged from 0.08 µg cm⁻² to 0.15 µg cm⁻².

Change in skin barrier function

Mean percentage changes in skin hydration results are depicted in Figure 2A. The percentage change in skin hydration varied on the different anatomical areas. Cutting

operators, sheet strappers and the weighbridge operator all showed an increase, though not statistically significant, in percentage change for skin hydration on all of the anatomic areas measured. An increase in the percentage change for skin hydration was observed for all areas except for the forehead where a slight, but not significant decrease was noted for the forklift drivers. Noted was the decrease in the percentage change for skin hydration of the plate washers for the index finger (27.58%), back of hand (33.33%) and forearm (8.33%), except for the forehead (17.26%) where a slight increase in percentage change occurred. For the forearm, percentage changes in skin hydration for the cutting operators and sheet strappers were 41.33% and 80.95% respectively.

Percentage changes in TEWL varied amongst different job categories. With the exception of the plate washer (index finger), increases in percentage change in TEWL ranged from 0.66% (forklift driver, index finger) to 76.98% (sheet strapper, forehead) (Figure 2B).

Percentage change in skin surface pH results are depicted in Figure 2C. For all job categories, except sheet strappers and plate washers, percentage change in skin surface pH decreased on all anatomical areas. Percentage change increases ranged from 1.43% (plate washer, index finger) to 7.23% (plate washer, forehead), while a decrease was observed ranging from 2.61% to 6.91% for forklift drivers. Percentage change in skin surface pH for cutting operators ranged from 1.30% to 6.58% and from 1.50% to 10.75% for weighbridge operators. Significant statistical differences for the percentage change were only found for the weighbridge operators. The pH of the index finger was significantly lower than that of the forehead, while that of the palm was significantly lower than that of the forehead. No significant difference was found between the index finger and the palm of the hand.

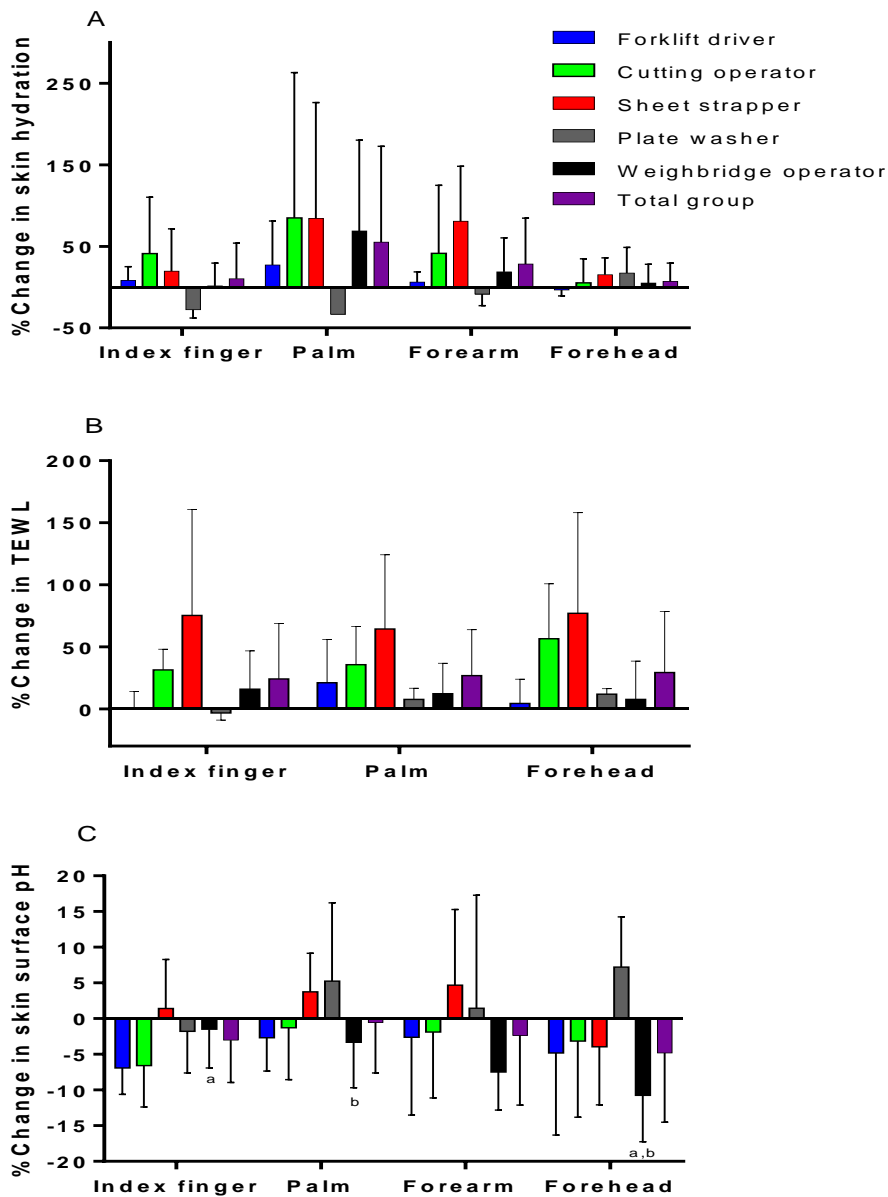


Figure 2. Percentage change in A) skin hydration, B) TEWL and C) skin surface pH from the beginning to the end of the work shift (mean \pm SD). Letters a and b indicates statistical significant differences ($p \leq 0.05$).

Skin questionnaire

Seven workers had a Dalgard score of > 1.3 which indicates an increased risk of developing skin diseases. The average Dalgard skin score according to the questionnaire for all workers was 1.24 ± 0.28 . From the seven workers that had a score

of > 1.3, three reported to have itchy skin (1 weighbridge operator, 1 sheet strapper, 1 cutting operator). One weighbridge operator reported that he had a dry/sore rash, while two reported that they had an itchy rash on their hands (weighbridge operator and sheet strapper). Two reported that they have pimples, but only during the last week (cutting operator and forklift driver). Two workers reported other rashes on their face (both weighbridge operators) and two workers reported other skin problems not listed in the questionnaire (both weighbridge operators). Three workers reported warts (all weighbridge operators), while six workers (2 forklift drivers, cutting operator, 2 weighbridge operators, 1 sheet strapper) reported troublesome sweating that started more than six months ago.

Discussion

The respiratory measurement results obtained were compared with the 8 hour nickel respiratory TWA-OEL of 0.5 mg m^{-3} , as stipulated in Table 2 of Chapter 22 Schedules, promulgated under the Mine Health and Safety Act. The mean exposure for the whole group was 12 times lower than the TWA-OEL, and 2.6 times higher than the 0.015 mg m^{-3} REL of NIOSH. Forklift drivers had the highest average respiratory exposure ($0.06 \pm 0.04 \text{ mg m}^{-3}$), probably due to the generation of secondary dust whilst operating the forklift.

The manual handling of nickel sheets was evident in this study. Only the forklift drivers handled the nickel sheets with a forklift, and not once was it observed that they manually handled the sheets. Detectable levels of nickel were present on all of the anatomical areas before the shift commenced. A previous study reported background levels of nickel on the hands of workers with a geometric mean of $0.02 \text{ } \mu\text{g Ni cm}^{-2}$ (Hughson *et al.*, 2010). Another study done by Du Plessis *et al.* (2010) reported background nickel exposure with a geometric mean of $0.782 \text{ } \mu\text{g cm}^{-2}$ ($1.033 \text{ } \mu\text{g cm}^{-2}$) for the index finger, $0.407 \text{ } \mu\text{g cm}^{-2}$ ($0.534 \text{ } \mu\text{g cm}^{-2}$) for the palm of the hand and $0.372 \text{ } \mu\text{g cm}^{-2}$ ($0.383 \text{ } \mu\text{g cm}^{-2}$) for the forehead. In this study the presence of higher nickel exposure levels are evident before the shift for the index finger and palm of the hand than previous studies. A reason being that the workers need to pass through the packaging section, before entering the tea room where morning briefings are held. The packaging area is also manually opened and forklifts are moved from where they were parked for the night, to a place where all the drivers can access the forklifts. Results of this study cannot be compared directly

with the results of Hughson *et al.* (2010) due to differences in anatomical sites and anatomical areas, but they may be compared to the results of Du Plessis *et al.* (2010), as the same sampling protocol and three of the four anatomical areas were used. Compared to the results of Du Plessis *et al.* (2010), nickel exposure for the index finger for this study were 1.32 times higher ($1.033 \mu\text{g cm}^{-2}$), 1.31 times higher ($0.534 \mu\text{g cm}^{-2}$) for the palm of the hand and 1.02 times higher ($0.383 \mu\text{g cm}^{-2}$) for the forehead for the before the shift measurements.

Dermal nickel exposure increased significantly from before the shift towards the end of the shift for the palm, forearm and forehead for the total group. Most of the significant differences resided from the forklift drivers as it was noted that they did not wear any personal protective equipment except for the two piece acid resistant overall and safety shoes. When operating the forklift no protective gloves were worn. Samples taken from the steering wheel and hand knob of the forklift showed high contaminated results ($0.4 \pm 0.15 \mu\text{g cm}^{-2}$) as well as further inspection of the employees' hands, where it was visibly dirty each time when skin wipes were taken. Although some of the job categories did show significant differences, it needs to be taken in account that with the small number of employees for each of the job categories, nickel exposure was variable. The variability in dermal exposure within job categories was also seen in studies done by Kromhout *et al.* (2004), Du Plessis *et al.* (2010), Hughson *et al.* (2010) and Du Plessis *et al.* (2013a). The high exposure levels in this study were most probably due to inadequate chemical protection provided by the gloves, as some of the inner gloves upon visual inspection were contaminated. These gloves that include the inner glove, are only changed at the workers own discretion.

The tea room is situated inside the work area, and workers need to pass through the work area for their morning meetings. Nickel on door handles, taps and tables and eating surfaces may possibly come into contact with the skin, even before the shift commences. Strapping and grading machines and drums were contaminated with nickel. Although no samples were taken in the change house in this study, Du Plessis *et al.* (2010) reported high levels of nickel on the counter where workers hand in their overalls after taking a shower, thus handling their contaminated overalls before they leave the workplace. This may possibly increase the risk of "take-home" contamination and also possibly expose their families at home to nickel.

Numerous factors influence skin hydration, skin surface pH and TEWL, that is branded as endogenous, exogenous, environmental and measurement-related factors. Age, anatomical position, sweating, skin temperature, ethnicity and skin health are the most important endogenous factors (Rogiers, 2001; Barel & Clarys, 2006; Farinelli & Bercardesca, 2006; Proksch *et al.*, 2008; Darlenski *et al.*, 2009; Jungersted *et al.*, 2010; Darlenski *et al.*, 2012). Solvents, surfactants, occlusion, skin washing and mechanical skin damage are all exogenous factors (Agache, 2004b; Kesic & Nielsen, 2009; Fluhr *et al.*, 2008; Voegeli, 2008; Kezic & Nielsen, 2009; Jungersted *et al.*, 2010; Du Plessis & Eloff, 2010; Du Plessis *et al.*, 2013b). Measurement and environmental factors include seasons, ambient temperature, relative humidity and air convection (Barel & Glarys, 2006; Tupker & Pinnagoda, 2006; Darlenski *et al.*, 2009; Du Plessis *et al.*, 2013b). Skin hydration, skin surface pH and TEWL as individual parameters are not always influenced by the same factors, and in some cases, the influence, if it is positively, negatively or not influenced at all, is debatable. In a controlled laboratory environment, exogenous and endogenous factors may serve as exclusion criteria for participation in studies, but in workplaces most of these factors are intrinsic to the workplace and workforce and if the same criteria are applied, workers would be unrepresentative of the actual work conditions and workforce (Du Plessis *et al.*, 2013a). Furthermore, no “golden rule” exists for the accurate interpretation and measurement of skin barrier function (Du Plessis *et al.*, 2010) and skin hydration, skin surface pH and TEWL measurements only rely on the standard reference values given by the manufacturers of these instruments. Of interest is the influence of the workplace or environment on skin barrier function of exposed workers. Recently published international guidelines recommend that TEWL, skin hydration and skin surface pH be reported as a percentage change (difference between before the shift and at the end of the shift) (Du Plessis *et al.*, 2013b; Stefaniak *et al.*, 2013).

Skin hydration is defined as the capacity of the stratum corneum to retain water (Sotoodian & Maibach, 2012). It was noted that skin hydration predominantly increased during the shift, but was highly variable amongst all the job categories. An increase in skin hydration can also be indicative of a deterioration in skin barrier function (Du Plessis *et al.*, 2013b). For the plate washers consistent decreases in the percentage change for skin hydration for all anatomical areas except the forehead was evident from the beginning till the end of the shift. At the end of the shift the percentage change increased

to higher levels than that of the baseline. Du Plessis *et al.* (2013a) found the same, where the skin hydration of cell-workers hands decreased during the shift, but increased to slightly higher levels than that of the before shift measurement. Increases were shown from the beginning of the shift to the end of the shift that ranged from 1.96% (palm of hand) to 7.48% (index finger), while for cutting operators in this study this ranged from 84.38% for the palm to 41% for the index finger (Du Plessis *et al.*, 2010). The variability between the studies may be contributed to different exposures and workplaces.

TEWL is a term used to describe the amount of water that passes from the internal body through the stratum corneum of skin to the external body surface and surrounding areas when there is no sweat gland activity (Mündlein *et al.*, 2008; Kezic & Nielsen, 2009). A disturbed or impaired skin barrier is indicative from an increased TEWL (Proksch *et al.*, 2008; Darlenski *et al.*, 2009). For this study an increased percentage change in TEWL was observed for most of the workers and subsequently most of the job categories, thus suggesting deterioration in skin barrier during the shift. This is in accordance with previous reports by Du Plessis *et al.* (2010) and Du Plessis *et al.* (2013), in which TEWL also increased throughout the shift.

The skin surface pH under normal conditions is regulated between 4 – 6, to maintain a constant internal homeostasis (Rippke *et al.*, 2004). An increase in skin surface pH could be an indication of a barrier that may be compromised or impaired. This should be seen in context as skin pH buffering is activated at lower pH (acidic) levels (Parra & Paye, 2003). It is evident from this study conducted that the percentage change in skin surface pH decreased through the entire shift for the forklift drivers, cutting operators and weighbridge operators. Results show high variability between sheet strappers and plate washers. A study done by Du Plessis *et al.* (2013) also showed a decrease in the percentage change of skin surface pH. The decrease in the percentage change of the skin surface pH is also of importance as it may influence dissolution of metals that come into contact with the stratum corneum. Dissolution of sensitizers, such as nickel, increases as sweat pH decreases (Hemingway and Molokhia, 1987; Emmet *et al.*, 1988; Haudrechy *et al.*, 1993; Haudrechy *et al.*, 1997; Du Plessis *et al.*, 2013). This may facilitate permeation of nickel through the skin and is perhaps only relevant to the plate washers as they are exposed to dissociable nickel salts, whereas the other job categories are exposed to metallic nickel.

Dalgard *et al.* (2003) self-reported skin questionnaire indicated that 37% of the workers stood a high risk of developing skin diseases, although all of them were of the opinion that they had healthy skin when asked what they thought of their skin. TEWL results in particular indicate an increase in the likelihood of a possible deterioration of the skin barrier during the shift, thus contradicting the self-reported score. Du Plessis *et al.* (2010) also found that workers at a base metal refinery, who are exposed to nickel, have a misperception of their own skin condition.

In this study, definite respiratory (although low) and dermal exposure was seen amongst base metal refinery workers: Predominantly, TEWL and skin hydration increased during the shift, suggesting that skin barrier function deteriorates during the shift. Gawkrödger *et al.* (2012) estimated a possible threshold of $0.035 \mu\text{g cm}^{-2}$ for sensitised individuals and $5.0 \mu\text{g cm}^{-2}$ for a single application of nickel to induce any dermatitis assessed over two days. This study showed no indication of allergic contact dermatitis, but exposure for the index finger was higher than $5.0 \mu\text{g cm}^{-2}$ for the forklift drivers as well as the plate washers, increasing the risk of possibly developing allergic contact dermatitis. Therefore, it can be speculated that the highest risk of exposure for respiratory exposure may be the forklift drivers. For dermal exposure the highest risk job category may be the plate washers as well as the forklift drivers.

Conclusion

Low respiratory nickel exposures at a packaging section of a base metal refinery were shown by this study. This study also indicated dermal nickel exposure. Nickel was detected on the index finger, palm, forearm and forehead for all job categories even before the shift had commenced. Surface wipe sampling indicated that areas such as tearoom eating tables and control rooms, door handles and operating machines are contaminated with nickel. The percentage change in skin hydration increased for most of the job categories except for the plate washers where a slight decrease was shown on the index finger, palm and forearm. Changes in TEWL and to a lesser extent skin hydration, suggest a deterioration in skin barrier function during the shift. A deteriorated barrier will most likely increase the permeability for nickel. However, results of this study did not indicate an inverse relationship between TEWL and skin hydration. Nickel together with other hazardous chemicals such as cobalt, are all found at a base metal refinery and are all known skin sensitisers. Co-sensitising of these hazards may increase

the risk of developing allergic contact dermatitis for all workers. For the skin surface pH, percentage change varied among job categories. The job categories possibly the highest risk in developing allergic contact dermatitis may be the plate washers as well as the forklift drivers. The skin condition together with high exposure levels of nickel on the skin are most probably caused by numerous factors: 1) Forklift drivers not wearing any protective gloves, 2) protective equipment upon visual inspection for all job categories was contaminated, 3) nickel was also detected on surfaces in the tea room (tea room door handle and surfaces), ablution facilities (basins and door handles), control room surfaces, drums, strapping and grading machines, forklift steering wheels and hand knobs. Recommended measures to lower respiratory and dermal exposure and increase skin barrier function are as follows: (i) wet methods to be used as housekeeping in place of sweeping, (ii) area demarcated for contaminated personal protection equipment storing with a basin, before entering the tearoom, (iii) automated opening and closing of tearoom doors, reduce contact to possible contaminated surfaces, (iv) improving hand wash facilities inside the packaging area, by implementing foot pedal water operating faucets, reducing contact with contaminated surfaces, (v) changes in operating procedures for cleaning of surfaces and areas, by implementing colour coding for cloths to be used in different areas, (vi) more frequent education and training sessions focusing on healthy skin, skin diseases, personal hygiene and the use of barrier creams, and (vii) encouragement to wear PPE and inspection to change personal protection equipment more regularly.

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CHAPTER 4
CONCLUDING CHAPTER

4.1 Introduction

In this chapter, a summary of the main findings from the article will be given. Objectives and hypothesis will be addressed. Challenges that existed in this study will be highlighted and possible future studies will be recommended. Recommendations to be considered with regard to control measures and the effectiveness thereof are indicated.

4.2 Summary of main findings and conclusion

The general aim of this study was to assess respiratory and dermal exposure of workers exposed to nickel in a packaging section of a base metal refinery. The specific objectives of this study were to: (i) assess dermal and respiratory exposure of workers exposed to nickel involved in packaging at a base metal refinery with the use of personal air sampling methods and Ghostwipes™ respectively; (ii) assess the percentage change in skin parameters (TEWL, skin hydration and skin surface pH) during a work shift in accordance to international guidelines, and workers will fill out a skin questionnaire; (iii) assess the surfaces that workers may come into contact with on a daily basis, by taking surface wipe samples using Ghostwipes™. This study addressed the aims and the results indicate low personal respiratory exposure ranging from $0.03 \pm 0.01 \text{ mg m}^{-3}$ to $0.06 \pm 0.04 \text{ mg m}^{-3}$. None of the exposure measurements exceeded the Occupational Exposure Limit (OEL) of 0.5 mg m^{-3} . Dermal nickel exposure was evident even before the shift had commenced on all anatomical areas measured for all job categories. Surface wipe sampling indicated that areas that workers may come into contact with on a daily basis are contaminated with nickel. Predominantly, changes in TEWL and to a lesser extent skin hydration, suggest a deterioration in skin barrier function during the shift. The percentage change in skin surface pH decreased for most of the job categories. Taking all the parameters into account and seen in context, a decrease in skin barrier function will most likely enhance the chances for nickel permeability through the skin. Forklift drivers together with plate washers may be the highest risk job categories in developing allergic contact dermatitis.

It was hypothesised that workers at a packaging section of a base metal refinery are exposed to quantifiable levels of nickel through the dermal exposure route.

The results confirm that workers at a base metal refinery are exposed to quantifiable levels of nickel through the dermal exposure route. Therefore the hypothesis is accepted.

4.3 Challenges of this study

Only a few challenges in this study were noted that could have influenced the measurement and interpretation of the results.

- Workers were hesitant to participate in this study as they felt the skin wipes were used to assess their personal hygiene of their skin.
- Although parts of this study formed part of the routine occupational hygiene monitoring programme of the base metal refinery, workers did not want to participate fully as they felt no results will be given to them.
- Workers completed a questionnaire as part of this study which indicated their perception of their skin condition. This, however, was not verified by medical records or medical examination by a dermatologist.

4.4 Future investigations

Detectable nickel was found even before the shift commenced, which may be attributed to more sources outside the packaging section. To obtain accurate dermal nickel exposure, surfaces of sampling areas should be cleaned thoroughly, to measure actual exposure for a specific shift.

At this specific base metal refinery, a new nickel tank house was built. Previous results of Du Plessis *et al.* (2010) at the old tank house, together with data from this study can be compared to the new tank house and packaging section, thus comparing “old” technology with “new” and improved technology.

As previously noted the perception of workers skin barrier function and actual measurements indicate different results. If future skin barrier function measurements are planned, a dermatologist should assist to examine skin health medically beforehand. A

dermal exposure and skin barrier function control sampling area or group is also recommended for future studies.

4.5 Occupational Hygiene Recommendations

Adequate and involved management together with control measures may improve the health and safety of workers and the enhancement of occupational hygiene practices at a base metal refinery, but is also a socio-economic responsibility as well as a South African legislation requirement. Recommendations for engineering, administrative and personal protective equipment (PPE) are as follows:

4.5.1 Engineering control

a) Automated opening and closing doors to the tea room can be installed, to reduce contact to possible surface exposure, such as door handles etc.

b) Washing facilities may be improved. Taps were broken, only cold water was available at the time of the study which may lead to a resistance of workers to continue with personal hygiene practices. This may also have an effect on contaminating other work or eating surfaces and increasing the risk of possible ingesting of nickel by the hand-to-mouth shunt. Taps may be contaminated when handled manually and may contribute to direct hand exposure.

- It is recommended that a foot pedal water operating faucet be installed for workers to wash their hands without using or touching taps.
- Provision of hot water may enhance the continuity of good personal hygiene practices

c) Wet methods are recommended as it was observed that housekeeping was done using sweeping with a broom as a method resulting in high secondary dust exposure. This will enable the workers to reduce dust exposure.

4.5.2 Administrative control

a) Changes in the operating procedures for cleaning of areas and surfaces are recommended. It was noted that the same water was used to clean eating surfaces and the floors, thus contaminating eating surfaces. Colour coding cloths for kitchens, ablution facilities and eating surfaces should be implemented.

b) Education and training should be done more regularly about the correct use of PPE and that PPE should be treated as contaminated. Education may be given to workers in the correct way to handle and remove contaminated PPE to reduce exposure at the workplace and at home. It was noted that forklift drivers did not wear any hand protection, and they should be encouraged to wear gloves when operating the forklifts although they do not manually handle the nickel sheets. Toolbox talk topics should include when to dispose of PPE.

c) Information and encouragement should be given to workers about good personal hygiene practices that they can use at work and at their homes, improving quality of life. This includes regular and effectively washing of hands and the use of emollient skin moisturizing creams to improve skin barrier function.

4.5.3 Personal Protective Equipment (PPE)

Personal protective equipment is the last resort of controlling exposure to any occupational hygiene hazard as its effectiveness is limited by a number of factors: i) The effectiveness is largely dependent on the user, ii) only the wearer is protected and iii) it can impede dexterity, vision, hearing and movement.

a) As best practice and according to procedure when doing housekeeping respiratory protection must be worn by all employees in the area. It was noted that only the sweeper wore his dust mask (FFP2), exposing his fellow workers to secondary dust emissions.

b) As previously mentioned gloves are only replaced at the discretion of the employee himself. Upon visual inspection the inner glove was dirty for all workers, thus re-exposure exists every day. It is recommended that the supervisor should inspect the workers inner gloves once a week, and that workers be encouraged to replace their inner gloves more often.

4.6 References

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English language editing certificate

ENGLISH LANGUAGE EDITING CERTIFICATION

This is to certify that the English language editing of this dissertation by Mr HJ Claassens was done by Prof. L.A. Greyvenstein.



LESLEY ANN GREYVENSTEIN (PROF)

P O Box 6601
Flamwood
Klerksdorp
2572

Tel: 018 468 7335/082 974 4505