Assessment of dermal exposure and skin condition of refinery workers exposed to selected metals

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This thesis is dedicated

in memory of two of my grandparents,

“Oupa Jan” and “Ouma Annie”

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Summary

Title: Assessment of dermal exposure and skin condition of refinery workers exposed to selected metals.

Aims and objectives: The research aims and objectives of this thesis were: (i) to review literature pertaining to different dermal exposure assessment methods; (ii) to assess dermal exposure of refinery workers to nickel and/or cobalt by making use of skin wipes as a removal method; (iii) to assess concurrently the skin condition of the above mentioned workers by measuring skin hydration, transepidermal water loss (TEWL) and skin surface pH, and (iv) to compare South African skin notations and sensitisation notations with those of other developed countries.

Methods: Refinery workers from two base metal refineries participated in this study. Skin condition and dermal exposure was measured on different anatomical areas before, during and at the end of a work shift. Dermal exposure to nickel and/or cobalt was assessed with Ghostwipes™ as a removal method. Wipe samples of potentially contaminated surfaces in the workplace were also collected. Wipes were analysed for nickel and/or cobalt according to NIOSH method 9102, using Inductively Coupled Plasma-Atomic Emission Spectrometry. The assignment and use of skin notations and sensitisation notations in South African legislation and six other developed countries were compared.

Results: To date, occupational dermal exposure has been reported for numerous substances by making use of surrogate skin methods (interception methods), removal methods and fluorescent tracer methods (*in situ* detection methods). From published literature it is evident that skin (dermal) wipes, as a removal method, are the most appropriate method to assess dermal exposure to metals. Varying degrees of skin dryness (low hydration indices) and impaired barrier function (high TEWL indices) are reported, with the hands being implicated the most. However, normal skin condition is also reported for some anatomical areas. Skin surface pH for all anatomical areas sampled decreased significantly during the shift, but remained in normal range. Dermal exposure to nickel occurred during the shift at the electro-winning plant of one refinery, while dermal co-exposure to cobalt and nickel occurred at the cobalt plant of the other refinery. At both of the refineries, cobalt and/or nickel was collected from the workers' skin even before the shift. Also, dermal exposure to these metals was highly variable between individual workers. Skin notations in South African legislation had a mean agreement of between 42.9% and 45.8% with other countries, while agreement for sensitisation notations was only 3.6% between countries.

Conclusions: Refinery workers are exposed to the sensitising metals, nickel and/or cobalt through the skin exposure route. The skin condition of refinery workers, in particular that of the hands, is indicative of unhealthy skin hydration and skin barrier function which may lead to increased dermal permeation and absorption of these metals and subsequently increase the risk of developing allergic contact dermatitis. Several measures to improve skin condition and to lower dermal exposure to nickel and/or cobalt are recommended. As with many other countries there is a lack of frequent review and updates of skin notations and sensitisation notations in South African legislation. Recommendations are made to improve the assignment and use of these notations.

Key words: dermal exposure, skin condition, nickel, cobalt, refinery, skin notation, sensitisation notation.

Opsomming

Titel: Bepaling van dermale blootstelling en velkondisie van raffinadery werkers blootgestel aan geselekteerde metale.

Doelstellings en doelwitte: Die navorsingsdoelstellings en -doelwitte van die tesis was: (i) om ’n oorsig van die literatuur met betrekking tot verskillende dermale blootstellings-assesseringsmetodes te gee; (ii) om dermale blootstelling van raffinadery werkers aan nikkel en/of kobalt te bepaal deur gebruik te maak van velveeglappe as ’n verwyderingsmetode; (iii) om ter gelyke tyd die velkondisie van bogenoemde werkers te bepaal deur velhidrasie, trans-epidermale waterverlies (TEWV) en vel oppervlak pH te meet, en (iv) om Suid-Afrikaanse velnoterings en sensitiseringsnoterings met dié van ander ontwikkelde lande te vergelyk.

Metodes: Raffinadery werkers van twee raffinaderye het deelgeneem aan die studie. Velkondisie en dermale blootstelling was gemeet op verskillende anatomiese areas, voor, gedurende en aan die einde van ’n werkskof. Dermale blootstelling aan nikkel en/of kobalt was bepaal met Ghostwipes™ as ’n verwyderingsmetode. Veegmonsters van potensieël-gekontamineerde oppervlaktes in die werksplek is ook versamel. Veeglappe was geanaliseer vir nikkel en/of kobalt volgens NIOSH metode 9102, wat gebruik maak van Induktiewe Plasma-Atomiese Emissie Spektrometrie. Die toewysing en gebruik van velnoterings en sensitiseringsnoterings in Suid-Afrikaanse wetgewing en ses ander ontwikkelde lande was met mekaar vergelyk.

Resultate: Tot op hede is dermale blootstelling vir talle substanse in die werkplek gerapporteer deur gebruik te maak van surrogaatvelmeetmetodes (onderskepmetodes), verwyderingsmetodes en fluoressensie-opspoordermetodes (*in situ* detektormetodes). Vanuit die gepubliseerde literatuur is dit duidelik dat vel (dermale) veeglappe, as ’n verwyderingsmetode, die mees toepaslike metode is om dermale blootstelling aan metale te bepaal. Wisselende grade van veldroogheid (lae hidrasie indekse) en beskadigde beskermingsfunksie (hoë TEWV indekse) word gerapporteer, met die hande die meeste aangedui. Normale velkondisie is egter ook gerapporteer vir sommige anatomiese areas. Vel oppervlak pH het betekenisvol afgeneem gedurende die skof vir alle anatomiese areas, maar het binne ’n normale reikwydte gebly. Dermale blootstelling aan nikkel het plaasgevind gedurende die skof by die elektro-herwinnings aanleg van een raffinadery, terwyl dermale ko-blootstelling aan kobalt en nikkel plaasgevind het by die kobalt aanleg van die ander raffinadery. By beide van die raffinaderye is kobalt en/of nikkel versamel vanaf die werkers se vel selfs voor die aanvang van die skof. Verder was die dermale blootstelling aan die metale hoogs veranderlik tussen individuele werkers. Velnoterings in

Suid-Afrikaanse wetgewing het ’n gemiddelde ooreenkoms van tussen 42,9% en 45,8% met die van ander lande gehad, terwyl die ooreenkoms vir sensitiseringsnoterings slegs 3,6% tussen lande was.

Samevatting: Raffinadery werkers word blootgestel aan sensitiserende metale, nikkel en/of kobalt, deur die velblootstellingsroete. Die velkondisie van raffinadery werkers, in besonder die hande, dui op ongesonde velhidrasie en velbeskermingsfunksie wat mag lei tot verhoogde dermale deurlaatbaarheid en absorpsie van die metale en gevolglik tot ’n verhoogde risiko vir die ontwikkeling van allergiese kontakdermatitis. Verskeie maatreëls om die die velkondisie te verbeter en om dermale blootstelling aan nikkel en/of kobalt te verminder, word aanbeveel. Soos in baie ander lande, is daar ’n gebrek aan gereelde oorsig en opdattering van velnoterings en sensitiseringsnoterings in Suid-Afrikaanse wetgewing. Aanbevelings word gemaak om die toewysing en gebruik van die noterings te verbeter.

Sleutelterme: dermale blootstelling, velkondisie, nikkel, kobalt, raffinadery, velnotering, sensitiseringsnotering.

Preface

This thesis is submitted in an article format in accordance with the General Academic Rules (rule A.13.7.3) of the North-West University. A chapter published in a handbook and four articles (three of which have been published), are included in this thesis:

- **Handbook chapter:** Badenhorst CJ, Du Plessis JL, Eloff FC. (2007) Chapter 12: Dermal Exposure. *In* Stanton, D.W., Kielblock, J., Schoeman, J.J., Johnston, J.R. editors. Handbook on Mine Occupational Hygiene Measurements. Johannesburg: The Mine Health and Safety Council. p.135-142. ISBN: 978 1 9198 5324 6.

- **Article I:** Du Plessis JL, Eloff FC, Badenhorst CJ, Booysen R, van Aarde MN, Laubscher PJ. (2008) Dermal exposure sampling methods: an overview. Occupational Health Southern Africa; 14(July/August):4-11.

- **Article II:** Du Plessis JL, Eloff FC, Badenhorst CJ, Olivier J, Laubscher PJ, van Aarde MN, Franken A. (2010) Assessment of dermal exposure and skin condition of workers exposed to nickel at a South African base metal refinery. Ann Occup Hyg; 54:23-30.

- **Article III:** du Plessis JL, Eloff FC. (2010) Dermal exposure and skin condition of workers co-exposed to cobalt and nickel at a South African base metal refinery. To be submitted to Ann Occup Hyg.

- **Article IV:** du Plessis JL, Eloff FC, Laubsher PJ, van Aarde MN, Franken A. (2010) Comparison of South African skin and sensitisation notations with other countries. Occupational Health Southern Africa; 16(May/June):18-24.

For the sake of uniformity, the reference style used in this thesis, with the exception of some of the published material, is that of the journal, Annals of Occupational Hygiene. Details on the requirements of the reference style can be found at the beginning of Chapter 5 of this thesis.

The contributions of the above listed co-authors and consent given for use in this thesis are given in Table 1. Permission from the relevant editors or publishers for use of the published material was granted. Proof thereof is given in Annexure A.

Table 1: Contributions of the different authors and consent for use

Author	Contributions of co-authors	Consent*
JL du Plessis	Responsible for the planning and design of the study under the supervision of Prof. FC Eloff. *Handbook chapter:* Wrote sections 12.4.1.1 (excluding parts of a-d), 12.4.1.2, 12.4.1.3 and 12.4.2 and gave a critical review of the rest of the chapter. *Articles I-IV:* Searched and reviewed literature, collected data, analysed data and interpreted results. Wrote the four articles (primary author) and thesis.	
FC Eloff	As Promotor of candidate planned and designed the entire study in collaboration with the candidate and Dr. CJ Badenhorst (articles I and II). *Handbook chapter:* Responsble for section 12.4.3 and gave a critical review of the rest of the chapter. Assisted with the interpretation of results and supervised the writing of the articles and thesis.	
CJ Badenhorst	Planned and designed part of the study (articles I and II). *Handbook chapter:* Principal author tasked with writing the chapter. Provided the broad framework for the sections of the text and wrote sections 12.3, 12.4.1.1a-d, 12.5 to 12.12.8. Gave a critical review of articles I and II as co-author.	
PJ Laubscher	Gave a critical review of articles I, II and IV as co-author.	
MN van Aarde	Gave a critical review of articles I, II and IV as co-author.	
J Booysen	Gave a critical review of article I as co-author.	
A Franken	Gave a critical review of article IV as co-author.	
J Olivier	Assisted with data collection and interpretation of results of article II.	

* I declare that I have approved the chapter/article(s) 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 the thesis of J.L. du Plessis.

The outline of the thesis is as follows:

- Chapter 1, the general introduction, gives some background, including the problem statement, hypothesis and aims of the study.
- Chapter 2 presents a literature study on topics relevant to this thesis.
- Chapters 3 to 7 present the published chapter in the handbook, the three published articles and one article to be submitted for publication.
- Chapter 8 makes conclusions with recommendations, limitations and possible future studies.
- Annexure A contains the permission letters for use of copyright material.

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Chapter 1: General introduction

1.1 Introduction

Nickel and cobalt are important commercial elements that are used in a wide variety of products and applications. Nickel is used to produce over 3000 alloys (including stainless steel), catalysts, rechargeable batteries, cooking utensils, corrosion-resistant equipment, coinage as well as in electroplating and welding (Winder, 2004; Liu *et al.*, 2008). Cobalt is also used in the production of various alloys, but moreover it is used in the production of cemented carbides, permanent magnets, prosthetics, jewellery, batteries, pigments, paint or varnish dryers and as catalysts (Winder, 2004; IARC, 2006; Liu *et al.*, 2008; Thyssen and Menné, 2010).

Occupationally, as well as among the general population, nickel is considered to be the most common cause of allergic contact dermatitis (Thyssen and Menné, 2010). Furthermore, the International Agency for Research of Cancer (IARC) recognises all nickel compounds as respiratory tract carcinogens in humans (Group 1), while metallic nickel is considered to be a possible human carcinogen (Group 2B) (IARC, 1990). Cobalt is also considered to be a common cause of allergic contact dermatitis (Liu *et al.*, 2008), but occupationally it is associated with bronchial asthma and hard-metal lung disease as well (ATSDR, 2004; IARC, 2006; Sauni *et al.*, 2010).

With a few exceptions, occupational hygiene has traditionally focused on inhalation exposure because it was generally considered to be the most important route of exposure (Schneider *et al.*, 2000; Semple, 2004). This meant that the other exposure routes, i.e. skin (dermal) contact and ingestion, were often overlooked (Sartorelli, 2002; Semple, 2004). Furthermore, the skin was incorrectly considered as an almost impermeable barrier to chemical substances until the mid-1960s (Sartorelli, 2002). In general, exposure by inhalation has been reduced in recent years due to well defined measurement methods, more efficient control measures and lower Occupational Exposure Limits (OELs). This, in turn, resulted in raising the general interest and importance of dermal absorption (Schneider *et al.*, 2000; McDougal and Boeniger, 2002; Sartorelli, 2002; Kielhorn, 2006) and to date, dermal exposure has been reported for numerous occupational and environmental chemical substances by making use of surrogate skin methods (interception methods), removal methods and fluorescent tracer methods (*in situ* detection methods) (Fenske, 1993; Brouwer *et al.*, 2000; Cherrie *et al.*, 2000; Soutar, 2000; Fenske, 2003; ECS, 2006).

Respiratory exposure of workers involved in the production (mining and refining) of metals and metal inorganic compounds, including nickel and cobalt is well documented. In contrast, only a limited number of dermal exposure studies for metals and their inorganic compounds exist. Assessment of

dermal exposure to nickel and cobalt is limited to a few studies, where exposure of carpenters, cashiers, locksmiths and workers involved in the production of cemented-carbides, gas turbines and space propulsion components were reported (Lidén *et al.*, 2008; Day *et al.*, 2009; Julander *et al.*, 2010). Only recently, Hughson *et al.* (2010) reported dermal exposure to nickel at European nickel production and primary user industries. However, there are no published data on dermal exposure to cobalt during production at refineries.

The skin acts as a physical barrier preventing loss of body fluids and penetration of chemical substances or infectious agents (Zhai and Maibach, 2002; Agache, 2004; Proksch *et al.*, 2008). This physical permeability barrier resides primarily in the stratum corneum (Pirot and Falson, 2004; Bouwstra and Ponec, 2006; Feingold, 2007) and is affected by various individual and environmental factors as well as diseases. Skin hydration and transepidermal water loss (TEWL) are two parameters commonly used to assess skin condition. Skin hydration reflects the skin's surface moisture level, while TEWL represents the total amount of water vapour lost through the skin under normal sweating conditions (Rawlings, 2006), and has been used extensively to evaluate skin barrier function (Zhai and Maibach, 2002; Pirot and Falson, 2004; Levin and Maibach, 2005; Rawlings *et al.*, 2008).

Damage to the skin, and thus a compromised skin barrier due to physical and mechanical irritation and chemical damage is suggested to be quite common in some occupational settings. Not only does compromised skin become more permeable for chemicals, but it may also facilitate absorption of irritants and allergens leading to further degradation of the skin barrier (Kezic and Nielsen, 2009). The influence of skin damage on dermal absorption of chemical substances has been studied extensively in experimental settings. Regrettably, only a limited number of workplace studies, not relevant to metals and the production thereof, have been reported. For nickel and cobalt, very limited reporting on skin absorption through intact skin has been done (Fullerton *et al.*, 1986; Hostynek *et al.*, 2001; Tanajo *et al.*, 2001; Larese *et al.*, 2007). Conversely, *in vitro* experiments conducted by Larese Filon *et al.* (2009) showed 84.87 and 92.90 fold increases in skin permeation through damaged (abraded) skin when compared to healthy skin for nickel and cobalt respectively. Furthermore, there is no published literature reporting the actual measurement of workers' skin condition upon exposure, and the subsequent use thereof in conjunction with dermal exposure assessment results.

Occupational exposure limits associated with inhalation exposure to chemical substances is well known. However, world-wide, no dermal OELs exist for any chemical substances, and in most cases the only legislation pertaining to dermal exposure is skin and sensitisation notations. Skin and sensitisation notations were intended only to serve as qualitative warning signs, respectively indicating that a specific chemical substance may penetrate the human skin with the potential of contributing significantly to total systemic toxicity (Sartorelli, 2002; Nielsen and Grandjean, 2004), or

that a chemical substance has the potential to produce sensitisation and thus allergic reactions (ACGIH, 2009). Assignment of skin notations between countries was proved to be inconsistently different (Fiserova-Bergerova *et al.*, 1990; Nielsen and Grandjean, 2004), but is not known for sensitisation notations.

1.2 HYPOTHESES

The following hypotheses are postulated:

Hypothesis 1: Refinery workers are exposed to sensitising metals (nickel and/or cobalt) through the skin exposure route.

Hypothesis 2: The skin condition of refinery workers is indicative of unhealthy skin hydration and skin barrier function, which may increase the risk of dermal absorption of nickel and/or cobalt measured on the skin.

1.3 RESEARCH AIMS AND OBJECTIVES

The aims and objectives of this thesis are:

1. to review literature pertaining to different dermal exposure assessment methods;
2. to assess dermal exposure of refinery workers to nickel and/or cobalt by making use of skin wipes as a removal method;
3. to assess concurrently the skin condition of the above mentioned workers by measuring skin hydration, TEWL and skin surface pH;
4. to compare South African skin notations and sensitisation notations published in the Regulations for Hazardous Chemical Substances (RHCS) and Mine Health and Safety Regulations (MHSR) with those of other developed countries in order to ascertain the assignment criteria and use of these notations relative to those of other countries

1.4 REFERENCES

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Chapter 2: Literature study

In the following sections published literature on topics relevant to this thesis will be construed. Firstly, nickel and cobalt as toxic metals and dermal sampling methods used to assess exposure in the workplace will be addressed. This will be followed by a brief description and discussion of the anatomy of the skin, skin barrier function and related parameters, and factors influencing skin (barrier) function. Finally, the world-wide use of, and limitations of skin and sensitisation notations in occupational exposure legislation will be discussed.

2.1 Nickel

More than three hundred nickel compounds and other substances containing nickel are known. Various oxidation states (0 to IV) can be found, but nickel (II) (Ni^{2+}) appears to be the only oxidation status relevant to aqueous chemistry (DEPA, 2008). This section of the literature does not aim to provide a comprehensive overview of nickel, but rather aims to highlight the commercial uses of nickel, the consequential human exposure and its associated health effects.

2.1.1 The commercial uses of nickel

Nickel is an extremely important commercial element. Physical-chemical properties that make nickel and its alloys valuable commercial commodities are its strength, corrosion resistance, good thermal and electric conductivity, magnetic characteristics, and catalytic properties (Liu *et al.*, 2008). Nickel is used in a wide variety of products and applications such as alloys (>3000, including stainless steel), catalysts, rechargeable batteries, cooking utensils, corrosion-resistant equipment, coinage, electroplating and welding (Winder, 2004; Liu *et al.*, 2008).

2.1.2 Exposure to nickel

Exposure to nickel may occur via the environment, as a consumer or occupationally (DEPA, 2008). For an extensive review the reader is referred to ATSDR (2005) and DEPA (2008).

2.1.2.1 Environmental exposure

Nickel is omnipresent in nature and the general public is exposed to low levels in air resulting from a combination of natural background sources (i.e. wind-blown dusts, volcanoes, etc.) and anthropogenic sources (nickel industry, combustion of fossil fuels, waste incineration etc.) (ATSDR, 2005; DEPA, 2008).

2.1.2.2 Consumer exposure

Consumers, i.e. the general public, are exposed to nickel in food, water, tobacco and its smoke and nickel-releasing/containing items (DEPA, 2008).

Nickel consumption through food and water has been estimated. In Europe it is estimated to be between 0.25 and 0.4 mg day^{-1} (Council of Europe, 2001 and United Kingdom Expert Group on Vitamins and Minerals, 2002 as quoted by DEPA, 2008).

Nickel is found in tobacco and tobacco smoke (DEPA, 2008) and is considered to be an unintentional route of exposure (ICMM, 2007). However, levels in the lower micrograms referred to by DEPA (2008) were all established almost two decades ago.

Of more concern is the high prevalence of nickel allergy in the general public due to exposure to nickel-releasing consumer items such as jewellery, coinage, buttons and zippers, cooking appliances, tableware, head sets, mobile phones and possibly makeup (DEPA, 2008; Thyssen and Menné, 2010). Various legislative controls, reducing the risk of consumer exposure by limiting nickel release from products, have now been introduced (DEPA, 2008).

2.1.2.3 Occupational exposure

Workers involved in the production of nickel through mining and refining processes are exposed to nickel through inhalation, dermal contact and inadvertent ingestion (Sivulka, 2005), while those using nickel containing products (hairdressers, bar staff, chefs and cooks, cashiers and catering staff) are exposed predominantly through direct dermal contact (Shum *et al.*, 2003).

Exposure can generally be classified as exposure to water soluble nickel compounds, water insoluble compounds or/and metallic nickel. The major water soluble nickel compounds are nickel acetate, nickel chloride, nickel sulphate (sulfate) and nickel nitrate. Important water-insoluble compounds are nickel sulfide, nickel subsulfide, nickel oxide, nickel carbonyl and nickel carbonate (Liu *et al.*, 2008).

Inhalation exposure levels in occupational settings are reported elsewhere and are beyond the scope of this thesis. Dermal assessment of occupational exposure to nickel is discussed in Section 2.3 of this chapter.

2.1.3 Absorption of nickel

2.1.3.1 Absorption following inhalation

Although influenced by numerous factors, available data suggest that 97 to 99% of soluble nickel compounds, with particles having an aerodynamic diameter < 5 µm (respirable fraction), are absorbed from the respiratory tract following inhalation. Non-respirable particles are cleared from the respiratory tract by mucociliary action and transferred to the gastrointestinal tract for possible absorption. Absorption of nickel metal, nickel oxides, nickel sulphides and nickel carbonate from the

respiratory tract is far more limited. Approximately 6% of metallic nickel is absorbed after inhalation (absorption from the respiratory tract and gastrointestinal system) (DEPA, 2008).

2.1.3.2 Absorption following oral intake

Approximately 25 to 27% of soluble nickel compounds were absorbed by fasting subjects after oral ingestion of drinking water containing these compounds, and 1 to 6% when subjects were non-fasting. For other nickel compounds the fraction that may be absorbed after oral intake is unknown due to limited data (DEPA, 2008).

2.1.3.3 Dermal absorption

Dermal absorption of substances is very complex and is influenced by many factors. For metals, it is comprehensively reviewed by Hostynek (2003). Individual factors such as age, gender, race/ethnicity, anatomical area and environmental conditions at the time of exposure may influence the dermal absorption of metals.

Several *in vitro* and *in vivo* studies investigated the dermal absorption of metallic nickel powders (oxidised by sweat to ionic form) and different nickel salts (Fullerton *et al.*, 1986; Hostynek *et al.*, 2001; Tanajo *et al.*, 2001; Larese *et al.*, 2007; Larese Filon *et al.*, 2009). From the available data it is clear that very limited skin absorption can take place through intact skin and large fractions of the applied dose remained on the skin surface (suggesting a very long lag-time) or in the stratum corneum (Fullerton *et al.*, 1986; Hostynek *et al.*, 2001; Tanajo *et al.*, 2001; Larese *et al.*, 2007). For risk assessment purposes, DEPA (2008) suggests 2% absorption of soluble nickel compounds and 0.2% for nickel metal through intact skin, while the International Council on Mining and Metals (ICMM, 2007) suggests 1% from full-shift exposure to liquid/wet media and 0.1% for dry (dust) exposure to metal cations. Conversely, *in vitro* experiments conducted by Larese Filon *et al.* (2009) showed a 84.87 fold increase in nickel skin permeation through damaged (abraded) skin when compared to healthy skin.

2.1.4 Distribution, cellular uptake and elimination after absorption

Nickel deposits have been found in lungs of exposed workers. Nickel ions, once in the bloodstream are transported in the serum as ultrafiltrable material (40%) and as a complex associated with albumin (34%) and nickeloplasmin (26%) (DEPA, 2008). The half life of nickel sulphate and nickel oxide in the human body is one to three days and more than 100 days, respectively (ATSDR, 2005). Insoluble nickel compounds enter cells via phagocytosis, while soluble compounds make use of passive diffusion and metal ion transport systems, in particular the magnesium transport system (DEPA, 2008). Data on concentrations of nickel in different human tissue is limited, but it appears that nickel

not excreted in urine is widely distributed in very low concentrations (IPCS, 1991 as quoted by DEPA, 2008). Ingested nickel is excreted via faeces (DEPA, 2008).

2.1.5 Human health effects

Inhalation is considered to be the most important route of exposure associated with its carcinogenic effects and other respiratory symptoms such as impaired lung function, chronic bronchitis, emphysema and fibrosis (ATSDR, 2005). In addition, nickel is considered to be the most common cause of allergic contact dermatitis (Salnikow and Zhitkovich, 2008). It is assumed that the determining factor in nickel toxicity is the nickel cation (Ni^{2+}) (Beyersmann and Hartwig, 2008; DEPA, 2008).

2.1.5.1 Carcinogenesis

The IARC recognised all nickel compounds as respiratory tract (lung, nasal cavity, paranasal sinuses) carcinogens in humans (Group 1), while metallic nickel is considered to be a possible human carcinogen (Group 2B) (IARC, 1990). This will be reaffirmed in the pending publication of volume 100 of the IARC Monographs (Straif *et al.*, 2009). As with other metals, it exerts its carcinogenic activity through indirect non-genotoxic mechanisms (Beyersmann and Hartwig, 2008; Salnikow and Zhitkovich, 2008). The three indirect mechanisms are related to nickel's ability to (i) induce formation of reactive oxygen species, (ii) interfere (inhibit) with DNA repair processes, and (iii) induce enhanced cell proliferation (Beyersmann and Hartwig, 2008). Furthermore, nickel is also considered to be a co-mutagen, and concurrent exposure to other genotoxic substances may enhance nickel's effects (Beyersmann and Hartwig, 2008; Salnikow and Zhitkovich, 2008).

2.1.5.2 Allergic contact dermatitis

Occupationally as well as among the general population nickel is considered to be the most common contact allergen. The most recent estimation indicates that up to 3% of men and 17% of women in the general population is allergic to nickel. The existence of a genetic predisposition to nickel allergy are debatable due to conflicting results (Thyssen and Menné, 2010). However, recently an association was made between loss-of-function mutations in the fillagrin gene (fillagrin prevents epidermal water loss and impedes entry of allergens and chemicals) and an increased risk for irritant contact dermatitis and nickel sensitisation (Novak *et al.*, 2008). This association emphasises the importance of the skin barrier in the development of occupational contact dermatitis (Kezic *et al.*, 2009; Thyssen and Menné, 2010).

Allergic contact dermatitis is a delayed type IV hypersensitivity reaction. Mechanistically two distinct phases are recognised, namely a sensitisation (induction) phase and an elicitation phase (DEPA, 2008; Thyssen and Menné, 2010). Sensitisation occurs through complex immunologic mechanisms, and in the case of nickel, it is induced by direct and prolonged dermal contact and skin permeation of nickel

ions (Vahter *et al.*, 2007; DEPA, 2008). As a hapten, nickel ions must react with proteins in the skin to form complete allergens. The complete allergens are internalised by Langerhans cells present in the epidermis (Karlberg *et al.*, 2008). After migration to the peripheral lymph nodes, the antigen is presented to T-lymphocytes (DEPA, 2008; Karlberg *et al.*, 2008). Over a period of about 14 days, antigen-specific effector and memory T-lymphocyte clones are formed, which thereafter circulate in the blood and lymph (DEPA, 2008). After sensitisation, any subsequent exposure to nickel (even to minute concentrations) will elicit an immune response, the elicitation phase, through recruitment of memory T-lymphocytes to the site of contact. Subsequent interactions between antigen presenting cells and T-lymphocytes take place in the epidermis and an inflammatory response develops within 24 to 48 hours (DEPA, 2008; Karlberg *et al.*, 2008; Alenius *et al.*, 2008). Erythema, edema, papules, vesicles and weeping are associated with acute dermatitis, while chronic dermatitis is scaly, dry and fissured (Peate, 2002; Thyssen and Menné, 2010). Also, individuals already sensitised to nickel have an increased risk of developing hand eczema (Vahter *et al.*, 2007), but the mechanistic connection between the two conditions is not understood (DEPA, 2008).

Allergic contact dermatitis is considered to be a chronic and potentially life-long condition. There is no cure for it and treatment is symptomatic through use of anti-inflammatory corticosteroids. Avoidance of contact with nickel is seen as the only true means of preventing relapses (DEPA, 2008; Karlberg *et al.*, 2008). To date, efforts to establish a scientific nickel salt threshold for skin sensitisation and elicitation caused by direct and prolonged skin contact has been unsuccessful, but for risk characterisation purposes in occupational scenario's a no observed effect level of 0.3 µg cm^{-2} is suggested (DEPA, 2008).

Exposure to nickel through ingestion or inhalation does not result in sensitisation, but widespread dermatitis has been reported in sensitised individuals following oral intake of nickel (Jensen *et al.*, 2003). However, other studies reported the development of immunological tolerance after oral intake of nickel, whereby sensitised individuals do not develop contact allergy after subsequent exposures (DEPA, 2008).

2.1.5.3 Respiratory effects

Limited data on occupational asthma due to exposure to nickel sulphate and metallic nickel exist, but no data exist for other soluble nickel salts. Therefore, nickel is considered as a potential respiratory sensitiser, but no threshold for sensitisation or elicitation currently exists (DEPA, 2008).

2.2 Cobalt

Cobalt exists in various oxidation states (0 to III), with cobalt(II) (Co^{2+}) being the most stable ion (Kim *et al.*, 2006). It is a nutritionally essential metal, and as cobalamin, it forms a critical component

of vitamin B_{12} which is required for erythrocyte production and the prevention of pernicious anemia (Liu *et al.*, 2008). Different radioactive isotopes of cobalt are used to sterilise medical equipment and as radiation therapy for treating cancer to name a few (ATSDR, 2004), but are beyond the scope of this thesis. The commercial uses, exposure and consequential health effects of cobalt will be discussed in the following text.

2.2.1 The commercial uses of cobalt

Cobalt is usually produced as a by-product of copper and nickel mining (Winder, 2004; Liu *et al.*, 2008). Due to its corrosion and wear resistance it is used in the production of various alloys and cemented carbides also known as hard-metals. Hard-metals (e.g. tungsten carbide) are primarily used in cutting and grinding tools. It is also used in permanent magnets, prosthetics, jewelery, batteries, pigments, as a paint or varnish dryer and as catalysts in the synthesis of heating fuels and alcohol (Winder, 2004; IARC, 2006; Liu *et al.*, 2008; Thyssen and Menné, 2010).

2.2.2 Exposure to cobalt

Cobalt exposure may occur via the environment, as a consumer or occupationally (IARC, 2006).

2.2.2.1 Environmental exposure

Cobalt occurs naturally in small amounts in soil, rock, air, water, plants and animals. It may enter the environment from natural sources and anthropogenic activities such as mining and refining, production and use of cobalt-containing alloys, coal-fired power stations and waste incinerators (ATSDR, 2004; Kim *et al.*, 2006).

2.2.2.2 Consumer exposure

The general public is exposed to very low levels of cobalt through inhalation, by drinking water and eating food containing it. Cobalt intake with food has been estimated to be 5 to 100 µg day^{-1} (ATSDR, 2004; IARC, 2006). Exposure may also be through skin contact with cobalt-releasing/containing products (ATSDR, 2004). Trace amounts of cobalt have been found in household products such as washing powders and liquids (Basketter *et al.*, 2003). Cobalt is also increasingly being used in dental alloys (Hosoki *et al.*, 2009 as quoted by Thyssen and Menné, 2010).

2.2.2.3 Occupational exposure

Occupational exposure is associated with the mining and refining of cobalt, the production of alloys, in the hard-metal industry that makes use of cutting and grinding tools and other industries that use cobalt or cobalt-releasing/containing products (ATSDR, 2004). Exposure may occur through inhalation and/or dermal contact (Bucher *et al.*, 1999; ATSDR, 2004; IARC, 2006). Cobalt allergy has been reported for hard-metal workers and glass and pottery painters (Rystedt, 1979; Fisher and

Rystedt, 1983). More recently, Athavale *et al.* (2007) indicated that hairdressers, builders/building contractors, retail cash/checkout operators, machine operators and domestic cleaners as occupations in the United Kingdom are most likely to develop cobalt-related occupational contact dermatitis, while in Italy Rui *et al.* (2010) associated textile and leather work as well as cleaning work with cobalt sensitisation.

Inhalation exposure studies, in particular exposure to hard-metals containing cobalt, are summarised in IARC (2006) and are beyond the scope of this thesis. Dermal assessment of occupational exposure to cobalt is discussed in Section 2.3.

2.2.3 Absorption of cobalt

2.2.3.1 Absorption following inhalation

Deposition of inhaled cobalt oxide in human lungs ranged between 50 and 75% for particles with a respective geometric mean diameter of 0.8 and 1.7 µm (ATSDR, 2004). Data on the actual respiratory absorption of cobalt following inhalation are scarce, but it was concluded indirectly, through urinary levels, that the absorption of soluble cobalt-containing particles (cobalt metal, cobalt salts and hard-metal) is more rapid than cobalt oxide particles. Insoluble particles were retained for longer periods in the lungs and may accumulate there (IARC, 2006).

2.2.3.2 Absorption following oral intake

In humans it is estimated that between 5 and 45% of cobalt is absorbed from the gastrointestinal tract after oral administration, with higher absorption associated with soluble cobalt (Liu *et al.*, 2008).

2.2.3.3 Dermal absorption

In vivo and *in vitro* dermal absorption of cobalt have been reported. Scansetti *et al.* (1994) reported dermal absorption indirectly after increased urinary cobalt levels were measured in four volunteers following dermal (hand) exposure to hard-metal dust containing approximately 5 to 15% cobalt metal. Similarly, skin absorption was also reported for five volunteers in a separate study by Linnainmaa and Kiilunen (1997).

In vitro studies indicated a very low skin permeation rate of metallic cobalt powder (oxidised by sweat). The permeation rate (0.0123 ± 0.0054 µg cm^{-2} h^{-1}) is comparable to that of nickel, but the lag-time of cobalt is 1.55 ± 0.71 hours compared with 14.56 ± 0.56 hours for nickel (Larese Filon *et al.*, 2004; Larese *et al.*, 2007). Larese Filon *et al.* (2009) showed a 92.90 fold increase in cobalt skin permeation through damaged skin when compared to healthy skin, meaning that even small injuries to the skin barrier can significantly increase skin absorption.

2.2.4 Distribution, cellular uptake and elimination after absorption

After absorption, cobalt is distributed systemically in blood. High concentrations have been found in the liver, kidneys, adrenal glands and thyroid (Liu *et al.*, 2008). Significant accumulation has been observed in the lungs after inhalation of insoluble particles (IARC, 2006). No information could be found on the cellular uptake of cobalt, but it should correspond with that of other metals. Excretion occurs in both urine and faeces (Liu *et al.*, 2008). Reported proportions and percentages differ significantly between sources (ATSDR, 2004; IARC, 200; Liu *et al.*, 2008), but urinary excretion is more likely for soluble cobalt and exposure through skin contact (ATSDR, 2004; Kim *et al.*, 2006). Insoluble cobalt and orally ingested cobalt are primarily excreted in faeces (Kim *et al.*, 2006).

2.2.5 Human health effects

Cobalt induces local and systemic health effects. Local effects in the skin and respiratory system are attributed to metallic cobalt-containing particles and/or solubilised cobalt ions, while toxic effects outside the respiratory system are more likely to be caused by cobalt ions (IARC, 2006). The underlying mechanism of cobalt toxicity is believed to be cobalt ions' ability to form reactive oxygen species in a Fenton type reaction. It is also proposed that tungsten carbide (hard-metal) catalyses electron transfer from metallic cobalt to oxygen and thus the formation of superoxide (ATSDR, 2004; Beyersmann and Hartwig, 2008).

2.2.5.1 Respiratory effects

Metallic cobalt-containing particles may cause mucosal irritation of the airways that may lead to rhinitis, sinusitis, upper respiratory tract inflammation and bronchitis (IARC, 2006). However, the main respiratory health effects of concern are bronchial asthma and hard-metal lung disease (Sauni *et al.*, 2010).

Inhalation of metallic cobalt, cobalt salts and hard-metals may cause respiratory sensitisation and consequentially induce bronchial asthma, an immediate type I hypersensitivity reaction in sensitised individuals. In workplaces bronchial asthma occurs more frequently than hard-metal lung disease (ATSDR, 2004; IARC, 2006; Sauni *et al.*, 2010).

Exposure to hard-metals containing metallic cobalt particles may cause interstitial hard-metal lung disease which was also referred to as hard-metal pneumoconiosis, tungsten-carbide pneumoconiosis, cobalt lung, cobalt pneumopathy and giant cell interstitial pneumonia in the past (IARC, 2006). It is a relatively rare occupational disease characterised by interstitial fibrosis and accumulation of giant cells in the alveolar spaces causing alveolitis (Kim *et al.*, 2006; Enriques *et al.*, 2007).

2.2.5.2 Allergic contact dermatitis

As with nickel, allergic contact dermatitis due to dermal exposure to cobalt is considered to be a delayed type IV hypersensitivity reaction (as discussed in Section 2.1.5.2) (ATSDR, 2004; Thyssen and Menné, 2010). Metallic cobalt and other cobalt compounds serve as allergens (IARC, 2006), though some evidence suggests that metallic metal is a more potent allergen than some of the cobalt salts (ATSDR, 2004). It usually manifests as eczema, usually of the hands, and erythema (ATSDR, 2004). Concurrent allergy to nickel and cobalt may also occur and it is considered to be due to co-sensitisation rather than cross-reactivity (Lidén and Wahlberg, 1994; Walhberg and Lidén, 2000). Co-sensitisation may predispose individuals to a greater extent and enhance the severity of dermatitis (Ruff and Belsito, 2006).

It is estimated that approximately 1 to 3% of the general population is allergic to cobalt (Thyssen and Menné, 2010), with a higher prevalence in women (Ruff and Belsito, 2006; Bordel-Gómez, 2010; Thyssen and Menné, 2010). In the 1970s and 1980s the higher prevalence was presumed to be due to contact with household products such as washing powders and liquids containing cobalt, but only trace amounts have been found in these products (Basketter *et al.*, 2003). The higher prevalence is more likely attributed to cobalt's presence in jewellery as an impurity in nickel alloys and is supported by a higher prevalence of cobalt allergy in pierced men when compared to non-pierced men. At present, Danish studies suggest that the prevalence of cobalt allergy among women is decreasing due to reduced exposure to nickel and cobalt from jewellery (Thyssen and Menné, 2010). Ruff and Belsito (2006) reported a higher prevalence of cobalt allergy in non-Caucasians. Increased age is also associated with cobalt allergy in men but not in women. In the United Kingdom, 4% of occupational contact dermatitis cases is attributed to cobalt, with a male to female ratio of 1:1 (Athavale *et al.*, 2007).

2.2.5.3 Carcinogenesis

In 2001 the IARC evaluated cobalt and cobalt compounds and classified the group as possible human carcinogens (Group 2B) due to inadequate evidence/data (IARC, 1991). However, in 2006 cobalt metal with tungsten carbide was classified as a probable human carcinogen (Group 2A), affecting the lungs, while cobalt metal without tungsten carbide, cobalt sulphate and other soluble cobalt(II) salts were classified as possible human carcinogens (IARC, 2006). The underlying mechanisms of mutagenicity are through the induction of oxidative stress and consequencial DNA damage and interference with DNA repair (Beyersmann and Hartwig, 2008).

2.2.5.4 Other health effects

In humans, high levels of cobalt chronically administered orally for treatment of anemia may cause goiter. Intravenous administration of cobalt can cause increased blood pressure, slow respiration,

tinnitus and deafness due to nerve damage (Liu *et al.*, 2008). Cobalt was also added as a foaming agent to beer in the 1960s, and the excessive intake of cobalt from drinking beer has been implicated in the development of cardiomyopathy with signs of congestive heart failure (Winder, 2004; Liu *et al.*, 2008). However, it is also possible that the cardiomyopathy may have resulted from protein-poor diets and alcohol abuse itself (ATSDR, 2004).

2.3 Methods of assessing dermal exposure to substances/contaminants

Various methods have been developed to assess dermal exposure to substances/contaminants. These methods can be grouped into three categories, namely (i) surrogate skin methods (or 'interception methods'), (ii) removal methods and (iii) fluorescent tracer methods (or '*in situ* detection' methods) (Fenske, 1993; Brouwer *et al.*, 2000; Cherrie *et al.*, 2000; ECS, 2006).

These methods are discussed in Chapter 3 of this thesis as part of a chapter of a handbook and as a review article. However, published literature assessing dermal exposure to nickel and cobalt will henceforth be analysed and evaluated.

2.3.1 Assessment of dermal exposure to nickel and cobalt

From the small number of publications it is evident that current knowledge of dermal exposure to nickel and even more so for cobalt, is very limited. A large majority of publications, due to the nature of exposure scenarios, assessed and reported exposure to nickel and cobalt and will be presented as such in the following section.

2.3.1.1 Assessment with a surrogate skin method

Roff *et al.* (2004) used cotton gloves and lightweight oversuits as a surrogate skin method to assess potential dermal exposure of workers exposed to electroplating fluids containing nickel, copper, chromium and zinc. After removal, segments of the gloves and oversuits were analysed by portable X-ray fluorescence spectrometry (PXRF).

2.3.1.2 Assessment with removal methods

Kristiansen *et al.* (2000) removed nickel from the skin of volunteers by means of tape stripping of the stratum corneum. They also determined levels of nickel in fingernails. Staton *et al.* (2006) developed a skin washing method, as a removal method, to assess dermal exposure to nickel associated with coin handling by immersing fingers in a washing solution.

Skin wipes, as a removal method, have been used to assess dermal exposure to antimony (Hughson, 2005a), beryllium (Day *et al.*, 2007), chromium (Lidén *et al.*, 2008a; Lidén *et al.*, 2008b; Day *et al.*, 2009; Julander *et al.*, 2010), cobalt (Lidén *et al.*, 2008a; Day *et al.*, 2009; Julander *et al.*, 2010), lead

(Hughson, 2005b), nickel (Lidén *et al.*, 2008a; Lidén *et al.*, 2008b, Day *et al.*, 2009; Hughson *et al.*, 2010) and zinc (Hughson and Cherrie, 2005). A summary of studies where nickel was removed from the skin of occupationally exposed workers through skin wiping is given in Table 1. A study of Lidén *et al.* (2008b) reporting skin exposure to nickel due to handling of Euro and Swedish coins was not included because its objectives are primarily aimed at nickel exposure of the general public handling coins, although reference is made to cashiers. Furthermore, only three volunteers participated in the study.

One of the major issues regarding assessment of dermal exposure is the lack of universally recognised and accepted standardised methods, and for nickel and cobalt this is quite evident from the studies summarised in Table 1. Major differences include the validation of a specific method (not listed in Table 1, but discussed in the following paragraph), the type of wipe used, the number of wipes per sample, the number of times an area must be wiped consecutively, the anatomical areas sampled, the surface area of samples and the measurement unit of results. The Nickel Producers Environmental Research Association (NiPERA) protocol for measuring workplace dermal exposure to metal particles, is based on the methodology of Hughson *et al.* (2010) (Adriana Oller, personal communication).

For all published studies there is a general agreement in establishment of the retention or analytical efficiency of a particular wipe by means of spiking wipes with known concentrations of metal powder or compounds and analysis thereof. However, for those studies reporting recovery efficiencies there are marked differences. Recovery efficiencies report the ability of the wipe in removing substances from the skin and are generally used to establish the number of wipes to be used and the number of times an area must be wiped. The issue here is the choice of medium to be used as a surrogate for human skin, because of limitations on *in vivo* testing. Lidén and collaborators (Lidén *et al.*, 2006; Lidén *et al.*, 2008a; Julander *et al.*, 2010) used a silicone rubber membrane as a surrogate for human skin and Hughson *et al.* (2010) used smooth cured leather for this purpose. They all reported recovery efficiencies above 90% by using three wipes, each wiped three consecutive times across the same area (Lidén *et al.*, 2006; Hughson *et al.*, 2010).

Hughson *et al.* (2010) assumed that workers' skin was clean and uncontaminated before commencement of a shift, while Day *et al.* (2009) collected pre-shift samples as a baseline. The last mentioned indicated the presence of nickel and cobalt in baseline samples which they attribute to handling of already-contaminated clothing or equipment prior to sampling or the occurrence of take-home exposure (contamination from the previous shift). Others reported cleaning of skin by means of washing and wiping prior to the shift (Lidén *et al.*, 2006; Lidén *et al.*, 2008a; Julander *et al.*, 2010).

Table 1: A summary of studies reporting removal of nickel and cobalt from the skin with wipes. All studies reported exposure to nickel and cobalt with the exception of Hughson *et al.* (2010) who only reported exposure to nickel.

Author	Occupational exposure scenario	Number of workers	Wipe used	Number of wipes and wipes per area	Anatomical areas sampled	Units of results
Lidén *et al.*, (2008a)	Carpenters Locksmiths Cashiers Secretaries (controls)	4 3 7 4	Paper-Pak wetted with 0.5 ml 1% HNO_3	3 wipes, each wiped 3 times over area. Collected on completion of task	Both hands Palm (7.5 cm^2 each) Finger tip thumb (2 cm^2 each) Finger tip index finger (2 cm^2 each) Finger tip middle finger (2 cm^2 each) Right hand Finger tip little finger (control)	µg cm^{-2} and µg cm^{-2} h^{-1}
Day *et al.*, (2009)	Cemented tungsten carbide production: Metal separation Powder handling Forming/machining	 12* 15 30*	Wash 'n Dri® wipe	1 wipe per area, area wiped for 1 minute by worker. Collected prior to shift and prior to lunch (mid-shift)	Both hands (palm and back of hand) Neck (ear-to-ear)	µg
Hughson *et al.*, (2010)	Refineries: Front-end refinery Electro-winning Packing of nickel metal Packing nickel compounds Packing nickel powder Powder metallurgy Stainless steel production	 6 12 7 14 6 8 13	Jeyes "sticky finger" wet ones	3 wipes, each wiped 3 times over area Collected prior to 2 breaks and at end of the shift. Face, neck and chest only collected at the end of the shift	Face (peri-oral area) Neck (25 cm^2) Chest (25 cm^2) Both hands: Back of hand (25 cm^2) Palm of hand (25 cm^2) Both forearms (25 cm^2 each)	µg cm^{-2}
Julander *et al.*, (2010)	Gas turbines and space propulsion components production: Tools sharpening Space propulsion components Thermal application	 8 8 8	Paper-Pak wetted with 0.5 ml 1% HNO_3	3 wipes, each wiped 3 times over area. Collected on completion of task	Forehead (9 cm^2) Dominant hand: Back of hand (9 cm^2) Palm of hand (9 cm^2) Finger tip thumb (2 cm^2) Finger tip index finger (2 cm^2) Finger tip middle finger (2 cm^2)	µg cm^{-2} h^{-1}

*Some workers were sampled more than once but on separate day.

Some of the studies included control subjects/workers, such as secretaries, and reported low levels of nickel contamination on the skin (Lidén *et al.*, 2008; Hughson *et al.*, 2010). A general trend of reported results is the high variability in the level of nickel and cobalt removed from the skin of exposed workers. Lidén *et al.* (2008) reported the highest nickel contamination for locksmiths 0.358 µg cm^{-2} h^{-1} (range: 0.053 - 0.629 µg cm^{-2} h^{-1}), with fingers more exposed than the palms of the hands. Cobalt exposure of all occupations was much lower, with a mean exposure of between 0.001 and 0.002 µg cm^{-2} h^{-1}. Day *et al.* (2009) reported that workers in the powder-handling facility had the highest nickel contamination (geometric mean), with 24 and 6 µg for the neck and hands respectively. Cobalt exposure was also the highest in the same facility and was also much higher than that of nickel, with 388 µg measured on the hands and 55 µg on the neck. They also reported a very good correlation for cobalt and nickel exposure. Julander *et al.* (2010) detected the highest levels of nickel on the skin of workers in the thermal application department with a median exposure equalling 0.62 µg cm^{-2} h^{-1} for the index and middle fingers (range: 0.034 - 15 µg cm^{-2} h^{-1}). The highest cobalt exposure occurred in the manufacturing of space propulsion components department, with a median exposure of 0.46 µg cm^{-2} h^{-1} (range: 0.0025 – 1.1 µg cm^{-2} h^{-1}) measured on the index and middle fingers.

The results of Hughson *et al.* (2010) are directly relevant to this thesis. For workers responsible for the electro-winning/electrolysis, hand and forearm total nickel exposure was measured to have a geometric mean of 0.56 µg cm^{-2} and a range of 0.16 to 3.19 µg cm^{-2}. For the neck and face (peri-oral), total nickel exposures were 0.25 µg cm^{-2} (< 0.02 - 2.21 µg cm^{-2}) and 0.58 µg cm^{-2} (< 0.02 - 4.32 µg cm^{-2}), respectively. Dermal exposure was also evident for other refinery processes, with packing of nickel powder having the highest overall dermal exposure, with a geometric mean of 8.73 µg cm^{-2} for the hands and forearms, 6.20 µg cm^{-2} for the neck and 15.16 µg cm^{-2} for the face. Dermal exposure in the front-end refinery, packing of nickel metal and other nickel compounds and primary user industries (magnet and stainless steel production) were much lower.

2.4 Skin anatomy, function and measurement of skin parameters

The skin anatomy will be described as a preamble to skin barrier function and measurable skin parameters such as stratum corneum hydration, TEWL and skin pH. This will be followed by a description and discussion of factors influencing the skin barrier function and measurement of the different skin parameters. Finally, methods for measurement of stratum corneum hydration, TEWL and skin surface pH are described.

2.4.1 Skin anatomy

The skin consists of an outer self-renewing epidermis which is separated from the underlying dermis of connective tissue by a basement membrane (McGrath *et al.*, 2004; Bouwstra and Ponec, 2006; Rice

and Mauro, 2008). The epidermis-dermis junction is undulating and ridges (rete ridges) of the epidermis project into the dermis. Not only does the junction provide mechanical support, but it also acts as a partial barrier against exchange of cells and large molecules (McGrath *et al.*, 2004). Hair follicles, sebaceous glands and eccrine glands span the epidermis and are all embedded in the dermis (Rice and Munro, 2008). The dermis provides a matrix in which polysaccharides and protein are linked to produce macromolecules with a very high capacity for water retention. A major constituent of the dermis is collagen, which provides great tensile strength. Cells such as fibroblasts, mast cells and histiocytes (monocytes/macrophages) are also found in the dermis. The dermis is richly supplied with blood, but no blood vessels pass through the dermal-epidermal junction. The dermis is separated from the underlying tissue by a layer of adipocytes (McGrath *et al.*, 2004).

The superficial epidermis consists of stratified squamous epithelial cells, mainly keratinocytes (McGrath *et al.*, 2004; Rice and Munro, 2008). Several other cells are also found within the epidermis, namely melanocytes, which donate melanin to keratinocytes, Langerhans' cells which have immunological functions, and Merkel cells (McGrath *et al.*, 2004). Keratinocytes, surrounded with aqueous intercellular fluid originate in the stratum basale (also known as the stratum germinativum) and move outward toward the skin surface while undergoing a two week programme of terminal differentiation. Four distinct morphological layers are formed in the epidermis by the transit of keratinocytes, namely the stratum germinativum, stratum spinosum, stratum granulosum and stratum corneum (McGrath *et al.*, 2004; Rice and Munro, 2008). The combination of the stratum basale and stratum spinosum is often referred to as the Malphighian layer (McGrath *et al.*, 2004). The stratum basale is generally considered to be a continuous mono-layer of small, cubic cells (McGrath *et al.*, 2004; Rice and Munro, 2008). The keratinocytes are tightly attached to each other by desmosomes and to the basement membrane by hemidesmosomes (Rice and Munro, 2008). Directly above the basal cell layer, enlarged keratinocytes form the spinous/prickle-cell layer, the stratum spinosum (McGrath *et al.*, 2004). Keratins, as insoluble intermediate filaments, account for approximately 40% of the total cell protein in the stratum spinosum (Rice and Munro, 2008). The stratum granulosum or granular layer is found above the stratum spinosum. Odland bodies or lamellar bodies/granules are found in the cytoplasm of keratinocytes of the upper spinous layer, which migrate to the periphery of the cells in the granular cell layer. Lamellar bodies discharge lipids into the intercellular spaces which play an important role in barrier function and intercellular cohesion within the stratum corneum (Madison, 2003; McGrath *et al.*, 2004; Bouwstra and Ponec, 2006). Keratinocytes undergo profound changes in their structure during the final steps of their differentiation and are transformed into flattened corneocytes of the stratum corneum (Proksch *et al.*, 2008). They have no nuclei, have a highly organised keratin sub-structure and have a cornified cell envelope. The cornified cell envelope is composed of a peripheral protein envelope just below the cell membrane and a covalently bound lipid envelope on the extracellular surface (exterior) of the corneocyte (Madison, 2003; Agache, 2004b;

Proksch *et al.*, 2008). Corneocytes are tightly packed and connected with adjacent cells by corneodesmosomes and are embedded in an intercellular matrix enriched in non-polar lipids organised as lamellar lipid bilayers (Agache, 2004b; Proksch *et al.*, 2008). The stratum corneum thickness ranges from 8 to 20 µm (except for the soles and palms), and consists of an average of six (genitalia) to 47 (extremities) layers of corneocytes (Agache, 2004b).

Desquamation or shedding of non-viable corneocytes takes approximately two weeks to complete and involves degradation of the intercellular lipids and intercellular corneodesmosome connections (McGrath *et al.*, 2004; Agache, 2004b, Rice and Munro, 2008).

2.4.2 Skin barrier function

The skin functions as a physical barrier preventing loss of body fluids (inside-out barrier) and penetration of chemicals or infectious agents (outside-in barrier) (Zhai and Maibach, 2002; Agache, 2004b; Proksch *et al.*, 2008).

This physical, permeability barrier resides primarily in the stratum corneum (Pirot and Falson, 2004; Bouwstra and Ponec, 2006; Feingold, 2007). The corneocytes, encased by a cornified envelope and cytoskeletal elements and corneodesmosomes provide mechanical strength to the skin, while a barrier to the movement of water and electrolytes is provided by the hydrophobic extracellular lipid matrix (Feingold, 2007; Proksch *et al.*, 2008; Jensen and Proksch, 2009). This organisation is commonly referred to as a "brick-and-mortar" array, with corneocytes representing the bricks and the intercellular lipids, the mortar.

The extracellular lipids of the stratum corneum have a unique composition and differ from typical lipids found in other biological membranes (Bouwstra and Ponec, 2006; Feingold, 2007). It is composed of long-chain ceramides (30-50%), cholesterol and free fatty acids (Pirot and Falson, 2004; Bouwstra and Ponec, 2006; Feingold, 2007; Proksch *et al.*, 2008). These lipids are secreted as polar precursors by lamellar bodies and are metabolised to non-polar lipids by co-secreted enzymes in the stratum corneum extracellular spaces (Feingold, 2007). The lipids are rearranged into multiple lipid lamellar bilayers positioned parallel to the cell surface, using the covalently bound lipid envelope of the corneocyte as a scaffold (Bouwstra and Ponec, 2006; Proksch *et al.*, 2008). The close interaction between ceramides and corneocyte cell envelopes creates a resistant and impermeable hydrophobic envelope which limits water diffusion across the corneocyte (Pirot and Falson, 2004).

More recently, Proksch *et al.* (2008) stated that the nucleated epidermal layers are also significant in the barrier function through its cell junctions (tight, gap and adherens junctions) as well as through desmosomes and cytoskeletal elements. According to Proksch *et al.* (2008), many researchers are of

the opinion that tight junctions may function as a rescue system when the stratum corneum is disturbed, challenged or absent, because secretion of tight junction proteins preceded the formation of the stratum corneum during epidermal regeneration.

Once the skin barrier is disrupted, through for instance tape-stripping or exposure to solvents, a rapid repair response is initiated to restore the barrier function. Within minutes, lamellar bodies from the outer stratum granulosum cells secrete their contents and new lamellar bodies will be formed. Concurrently cholesterol and fatty acids will also be synthesised in the epidermis (Feingold, 2007). The barrier repair response is triggered by a change in the extracellular calcium ion concentration surrounding the stratum granulosum cells. Immediately after skin barrier disruption, increased water movement carries this calcium toward the skin surface, decreasing the extracellular concentration and inducing lamellar body secretion. The release of cytokines (interleukins and tumour necrosis factor) secreted by the stratum corneum and keratinocytes upon barrier disruption is also of importance (Feingold, 2007; Proksch *et al.*, 2008; Fluhr *et al.*, 2008a).

2.4.3 Stratum corneum hydration

The water content of the stratum corneum is necessary for proper differentiation and desquamation (Verdier-Sévrain and Bonté, 2007) as well as maintenance of the skin barrier (Fluhr *et al.*, 2008a). Normal hydration levels range between 20 and 30% in the lower half of the stratum corneum, but decrease to between 5 and 10% near the surface (Agache, 2004b). Within corneocytes, water is thermodynamically considered to be free or weakly or strongly bound to lipids and proteins (Bernengo and de Rigal, 2004). Water in the deeper layers is tightly bound to the protein, filaggrin. However, filaggrin disintegration is rapid and it releases water and hygroscopic low molecular weight substances into the cytoplasm. Water is retained in corneocytes by forming weak bonds with these hygroscopic substances. There is an increase in the permeability of corneocyte cell membranes in the upper layers of the stratum corneum, possibly due to proteolytic enzymes, which results in the progressive loss of these hygroscopic substances and the dehydration of corneocytes. Water in the intercellular spaces is free or very weakly bound to polar groups of ceramides and other amphiphilic lipids. The lower atmospheric relative humidity attracts this water to the surface (Agache and Black, 2004).

2.4.4 Transepidermal water loss (TEWL)

The transepidermal water loss (TEWL) represents the flux density (g m^{-2} h^{-1}) of water diffusing through the stratum corneum from the viable epidermis to the surrounding atmosphere (Imhof *et al.*, 2009). TEWL is also referred to as *Perspiratio insensibilis*, and should not be confused with perspiration or sweating (*Perspiratio sensibilis*) (Gabard and Treffel, 2004; Tupker and Pinnagoda, 2006). When convective current is absent, the human body is in essence surrounded by a layer of water vapour, which is transferred from the skin surface to the surrounding atmosphere (Agache and

Black, 2004; Gabard and Treffel, 2004; Tupker and Pinnagoda, 2006). TEWL is not visible to the naked eye and amounts to approximately 300-400 ml day^{-1} for normal skin (Gabard and Treffel, 2004).

TEWL measurement has been used extensively to evaluate skin barrier function (Zhai and Maibach, 2002; Pirot and Falson, 2004; Levin and Maibach, 2005; Rawlings *et al.*, 2008). Proksch *et al.* (2008) state that many dermatologists and researchers believe that TEWL itself is the barrier, but measured TEWL is only a marker of the inside-outside barrier. The inside-outside barrier often correlates with the outside-inside barrier, but there are a few exceptions. However, mainly due to ethical considerations determination of the outside-inside barrier function through human penetration studies is not possible. There is a substantial amount of data that confirms a relationship between TEWL and skin penetration, but it cannot be fully generalised (Levin and Maibach, 2005).

There is an inverse relationship between TEWL and stratum corneum hydration. A disturbed barrier function is marked by a high TEWL, which is often correlated with a low hydration of the stratum corneum (Proksch *et al.*, 2008). However, the mechanism is not known. It is believed that disturbed barrier function leads to changes in epidermal differentiation, which influences filaggrin break-down products (release of water).

2.4.5 Skin surface pH

The pH is defined as the negative logarithm (base ten) of the concentration of free hydrogen ions in an aqueous solution (Agache, 2004b, Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006).

Skin surface pH is considered to be an important regulator of the formation of the skin barrier and control of resident microbes, but also prevents colonisation by pathogenic microbes (Agache, 2004b; Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006). An optimal pH is required to activate lipid enzymes responsible for processing secreted lamellar bodies and, therefore, the formation of the skin barrier (Fluhr *et al.*, 2006; Feingold, 2007).

The skin surface pH ranges between 4.2 and 6.1, depending on the anatomical area, but there are physiological holes or gaps, found at the axillae, genitoanal region and interdigital areas, where the pH is closer to seven (Agache, 2004b, Schmid-Wendtner and Korting, 2006). A rising pH gradient exists between the skin surface and further into the epidermis, where the body's internal pH is reached at the stratum granulosum (Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006). It is suspected that the pH gradient is important in controlling enzymatic activities and skin renewal (Schmid-Wendtner and Korting, 2006; Feingold, 2007). The precise origin of the acid mantle is still unclear, but it is believed

to be created by the interactions between components of the stratum corneum and interactions with secretions from sweat and sebaceous glands (Schmid-Wendtner and Korting, 2006; Tobin, 2006).

2.4.6 Factors affecting the skin and skin barrier function

Variation in the skin and its barrier function are attributed to various individual and environmental factors as well as diseases (dermatoses). Although occupational exposure to substances is subjected to the environmental conditions under which exposure occurs it will be considered separately. A short discussion of the most important factors affecting skin hydration, skin pH, TEWL and measurement thereof, in particular those relevant to this thesis, will be given in the following text.

2.4.6.1 Individual factors

Individual factors that may affect the skin and its function are age, gender, race/ethnicity, anatomical area and sweating and skin temperature.

2.4.6.1.1 Age

Skin aging is characterised by structural and morphological changes (Makrantonaki and Zouboulis, 2008). During the aging process, both TEWL and skin hydration decrease in a directly proportional relationship. The decrease of TEWL is highly evident after the age of 60 years (Farinelli and Berardesca, 2006), and may, therefore, be a factor to consider in occupations where potentially exposed workers retire beyond the age of 60 years. Skin surface pH is elevated in aged persons (Fluhr *et al.*, 2006)

2.4.6.1.2 Gender

According to Fluhr *et al.* (2008a), gender has no influence on either stratum corneum hydration or TEWL. Gender-related differences in skin surface pH are conflicting, with some reporting a more acidic pH in women, while others reported no differences (Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006).

2.4.6.1.3 Race/Ethnicity

Skin function data relating to different races and ethnic groups are often conflicting (Fluhr *et al.*, 2008b).

The stratum corneum has a similar thickness in black and white skin. However, black stratum corneum contains more cell layers with greater intercellular cohesion (reflected by increased electrical resistance) and increased lipid content. Corneocyte surface area is of equal size in black and white stratum corneum, but desquamation was reported to be higher in the stratum corneum of black skin

possibly due to lower intercellular ceramides levels (Berardesca and Maibach, 2003; Rawlings, 2006; Fluhr *et al.*, 2008b).

In vitro measurements of TEWL were significantly higher for black than white skin. Higher TEWL was also measured for black skin *in vivo*, but other results did not indicate any ethnic differences in TEWL (Berardesca and Maibach, 2003). Skin barrier function is considered to be stronger for darker skin upon mechanical and chemical challenge (Rawlings, 2006). Recovery of the epidermal barrier after acute disruption by tape stripping was significantly higher in blacks (Berardesca and Maibach, 2003). Some studies reported differences in stratum corneum hydration levels between ethnic groups, while others reported none (Fluhr *et al.*, 2008b). Ethnic differences in skin pH have been demonstrated, with black skin having a lower pH than white skin (Schmid-Wendtner and Korting, 2006; Fluhr *et al.*, 2008b).

Ethnic differences in the susceptibility and prevalence of skin dermatoses have been reported (Fluhr *et al.*, 2008b). Black skin is less susceptible to irritants (Farinelli and Berardesca, 2006). Although reports on the incidence of allergic contact dermatitis in blacks are conflicting (Berardesca and Maibach, 2003), Dogliotti (1970) reported lower incidences in black South Africans.

2.4.6.1.4 Anatomical area

The stratum corneum thickness is not uniform across the whole body, with the palms of the hands and soles of the feet being the thickest and the scrotum the thinnest (Farinelli and Berardesca, 2006). There are large variations in stratum corneum hydration across different anatomical areas, with higher values associated with the forehead and palm of the hand, while lower values are associated with the abdomen, thigh and lower leg (Barel and Clarys, 2006).

Variation in TEWL and skin surface pH across different anatomical areas is also well known (Agache, 2004b; Farinelli and Berardesca, 2006; Schmid-Wendtner and Korting, 2006). The variation in TEWL is likely to be attributed to the regional variation in the total lipid content of the stratum corneum (Farinelli and Berardesca, 2006).

2.4.6.2 Environmental factors

Environmental temperature and relative humidity, and their seasonal variation, are the most prominent environmental factors affecting skin hydration and TEWL.

The skin as a thermoregulatory organ, controls body temperature by regulating the rate of blood flow through dermal capillaries and sweat secretion. The body responds to an increase in environmental temperature by increasing blood flow through dilated dermal capillaries and increased sweat

production and secretion by sweat glands. Through evaporation, sweating leads to a loss of skin surface heat. Sweating is associated with increased hydration of the stratum corneum. However, high ambient humidity prevents sweat evaporation and thus also leads to increased stratum corneum hydration (Goh, 2006). Seasonal variation, where higher hydration is measured in summer due to higher environmental temperature and relative humidity, has been reported (Barel and Clarys, 2006).

Because of the dependency of TEWL on the water vapour pressure gradient on the skin surface it is easily influenced by sweating. The influence of normal sweating on TEWL measurements can be eliminated by conducting measurements in a controlled environment after adapting subjects to the environmental conditions (Gabard and Treffel, 2004). TEWL will increase with an increase in environmental temperature, with an increase from 22 to 30 ºC almost doubling TEWL (Tupker and Pinnagoda, 2006). On the other hand TEWL will decrease with an increase in environmental relative humidity (Gabard and Treffel, 2004).

TEWL and stratum corneum hydration measurements are easily affected by air convection and turbulence. Air turbulence and convection in close proximity to the measuring probe can be eliminated by conducting measurements in a specifically designed enclosure (Gabard and Treffel, 2004).

2.4.6.3 Occupational exposure

Damage to the skin and a compromised skin barrier due to physical and mechanical irritation and chemical damage (water, solvents and detergents) is common in occupational settings such as health care, metal machining, food preparation, printing, hairdressing, cleaning and the rubber industry. The influence of skin damage on dermal absorption has been studied extensively in experimental settings. Unfortunately, only a limited number of workplace studies have been reported. Compromised skin not only becomes more permeable to chemicals but it may also facilitate absorption of irritants and allergens leading to further degradation of the skin barrier. Larger compounds such as proteins and nanoparticles, usually not permeable through intact skin, may also be absorbed through damaged skin (Kezic and Nielsen, 2009).

The mechanisms of skin barrier alteration by solvents, surfactants, mechanical factors and increased hydration will be discussed in the following text.

2.4.6.3.1 Solvents

Organic solvents are frequently used as degreasers and cleaning agents. It is suggested that organic solvents increase skin permeability (disruption of the skin barrier) by extracting intercellular lipids from the stratum corneum and alteration of lipid bilayers structure (Fluhr *et al.*, 2008a; Kezic and

Nielsen, 2009). Desmosomes may also be damaged which may lead to partitioning of the stratum corneum and a reduction in barrier function (Kezic and Nielsen, 2009).

2.4.6.3.2 Surfactants

Sodium lauryl sulphate (SLS) is a well known surfactant used in soaps and cleansers and pharmaceutical studies. Surfactants affect the skin barrier by interacting with skin lipids and proteins leading to disorganisation of the lipid bilayers, reduced corneocyte cohesion and decreased moisture of the stratum corneum (Nielsen, 2005; Kezic and Nielsen, 2009).

2.4.6.3.3 Mechanical factors

Scrubbing, skin friction or abrasion may partially or completely remove the stratum corneum and thus disrupt the skin barrier by exposing the viable and water-rich epidermis to the environment (Fluhr *et al.*, 2008a; Kezic and Nielsen, 2009). Increased stratum corneum hydration is associated with tape stripping, which is commonly used to induce acute mechanical skin irritation (Fluhr *et al.*, 2008a).

2.4.6.3.4 Occlusion, wet-work and skin washing/cleaning

Occlusion is of occupational relevance through prolonged wearing of protective clothing, especially protective gloves, while washing and prolonged contact with liquid/water is associated with occupations requiring frequent cleaning of the skin and wet work. At present, the precise mechanism of permeability enhancement by water is not fully understood (Kezic and Nielsen, 2009).

Occlusion of the skin surface contributes to skin hydration, whereby TEWL is blocked, leading to a filling and dilatation of intercellular spaces across the whole stratum corneum. This is followed by a deceleration of water loss from the deepest corneocytes, passive hydration and swelling of corneocytes. This hyper-hydration of the stratum corneum reduces the skin barrier properties of the skin (Zhai and Maibach, 2002). If occlusion is prolonged, equilibrium may be reached between the water concentration within the stratum corneum and the viable epidermis (Agache and Black, 2004). Even short periods of occlusion can significantly increase stratum corneum hydration (Zhai and Maibach, 2002). Morphological changes of the skin surface have been demonstrated in skin occluded for 24 hours (Zhai and Maibach, 2002).

Health care workers, hairdressers and cleaners are occupations associated with wet work. Upon contact with the skin, water permeates the intercellular spaces, crosses cell membranes and the corneocytes swell (Agache and Black, 2004). It was proved that the stratum corneum is able to absorb more than its dry weight in additional water when immersed or placed in a wet environment (Agache, 2004b). Frequent and/or prolonged contact with water will, therefore, disrupt the skin's lipid bilayers and reduce corneocytes' cohesiveness and enhance the permeability of substances. Furthermore, skin

pH is also affected by skin cleaning, and a rise in pH has been observed after washing with alkaline soaps and even with tap water (Schmid-Wendtner and Korting, 2006).

2.4.6.4 Dermatoses

To date, several skin diseases with abnormalities in barrier function and altered lipid composition and organisation have been identified (Madison, 2003; Bouwstra and Ponec, 2006; Proksch *et al.*, 2008; Jensen and Proksch, 2009). However, a detailed discussion thereof is beyond the scope of this thesis.

Inflammatory skin diseases such as irritant and allergic contact dermatitis are also associated with skin barrier disruption (Proksch *et al.*, 2006; Proksch *et al.*, 2008). Irritants impair barrier function by removing lipids or disruption of intercellular lipid organisation in the stratum corneum. This facilitates penetration into the viable epidermis, where cell membranes of keratinocytes are damaged and lipid secretion by lamellar bodies and subsequent extracellular transformation thereof is disrupted. This leads to irritant contact dermatitis associated with ongoing skin barrier function impairment and inflammation (Proksch *et al.*, 2006). A defective barrier function is considered to be the primary event enabling allergen penetration into the skin and consequential initiation of immunological reactions and inflammation (Proksch *et al.*, 2008). Irritant dermatitis very often precedes allergic contact dermatitis (Proksch *et al.*, 2006).

Changes in skin pH were indicated in the pathogenesis of skin diseases such as irritant contact dermatitis and atopic dermatitis to name a few (Schmid-Wendtner and Korting, 2006), thus validating measurement of skin surface pH.

2.4.7 Methods for measurement of stratum corneum hydration, TEWL and skin surface pH

Numerous methods are available to measure stratum corneum hydration and TEWL. With the exception of TEWL, only methods used in this study to measure stratum corneum hydration and skin surface pH will be discussed henceforth.

2.4.7.1 Measurement of stratum corneum hydration

The electrical properties of the skin are dependent on the water content of the stratum corneum (Pirot and Falson, 2004; Gabard *et al.*, 2006), but can also be influenced by ions, glycerine and emollients to name a few (Gabard *et al.*, 2006). Skin hydration is, therefore, measured as the total impedance (or electrical opposition to an alternating current) applied to the skin, where the total impedance depends on the contribution of resistance and capacitance. The Corneometer (Courage and Khazaka, Germany) measures the capacitance contribution of the skin in contact with the measuring electrode (Barel and

Clarys, 2006). Changes in capacitance are expressed as arbitrary hydration units, with lower values (typical of weak electrical conductance) associated with dry skin.

Hydration measurements are influenced by instrumental, individual and environmental factors (Barel and Clarys, 2006). A comparison of the different hydration measuring instruments commercially available and their accuracy and precision is beyond the scope of this study, and the reader is referred to Barel and Clarys (2006) and Gabard *et al.* (2006) for a detailed discussion. Individual and environmental factors are discussed in Sections 2.4.6.1 and 2.4.6.2, respectively.

2.4.7.2 Measurement of TEWL

TEWL can be measured by using an open-chamber method or closed-chamber method. Open-chambers are open to the surrounding atmosphere and thus are easily influenced by external air convection and turbulence (Gabard and Treffel, 2004). Closed-chamber methods are more recent developments in which the measuring chamber is enclosed from the surrounding atmosphere.

TEWL can be calculated by measuring the water vapour pressure gradient at the skin surface, which is considered to be constant in the absence of external convection currents. In the open-chamber method, the vapour pressure gradient is calculated by measuring the difference in vapour pressure between two distinct points aligned perpendicularly to the skin surface. The vapour pressure is calculated as the product of relative humidity and saturated vapour pressure, which is dependent on temperature. The relative humidity is measured using capacitive sensors, while temperature is measured with fast thermistors. The sensors are located in a handheld cylindrical measuring chamber (diameter of 0.8 to 1 cm^2) with open ends. One open end is placed on the skin, while the other acts as an exhaust to allow water vapour to escape to the atmosphere. (Pirot and Falson, 2004; Tupker and Pinnagoda, 2006; Imhof *et al.*, 2009). Continuous measurement of TEWL is possible, but long measurement times are common. The EDS12 measurement system (Enviroderm Services, United Kingdom) is based on the Tewameter (Courage and Khazaka electronic GmbH, Germany) open-chamber system.

Two types of closed-chamber methods are available, namely a condenser chamber method and an unventilated-closed chamber method. With the condenser-chamber method, the small measurement cylinder is closed off at the top by a condenser. The temperature in the condenser is kept below the freezing point of water, creating a humidity gradient that causes water diffusion away from the skin surface. Measurement sensors are located in the wall of the cylinder and in the condenser. Continuous measurements are possible with condenser-chamber type instruments. With the unventilated-chamber method, the measuring cylinder is also closed off at the top. When placed on the skin, water vapour pressure from the skin collects in the chamber and with time the humidity in the chamber will

increase, slowly at first thereafter linearly. Flux density (TEWL) is calculated from the change in relative humidity and temperature over time (Imhof *et al.*, 2009). Due to the accumulation of water vapour and humidity these instruments must be purged after each measurement and cannot be used for continuous measurements (Tupker and Pinnagoda, 2006; Imhof *et al.*, 2009). However, the measurement time of unventilated-closed chamber instruments is very short (< 10 seconds) (Nuutinen, 2006). The Vapometer (Delfin Technologies Ltd, Finland) is an example of an instrument using the unventilated-closed chamber method (Gabard and Treffel, 2004).

TEWL measurement is influenced by instrumental, individual and environmental factors (Gabard and Treffel, 2004; Tupker and Pinnagoda, 2006). Recent developments and improvements have led to a reduction in the instrumental factors as sources of errors and variation. However, environmental factors and individual factors are responsible for the greatest variations (Section 2.4.6).

2.4.7.3 Measurement of skin surface pH

Skin surface pH is commonly measured with a flat glass electrode coupled to a potentiometer (Fluhr *et al.*, 2006), but can also be measured using pH-sensitive fluorescent dyes (Fluhr *et al.*, 2008a)

2.5 Legislation pertaining to occupational skin exposure

The only South African legislation relating to occupational skin exposure is the skin and sensitisation notations that accompany the OELs of hazardous chemical substances in the Regulations for Hazardous Chemical Substances (1995) under the Occupational Health and Safety Act (Act 85 of 1993) and the Mine Health and Safety Regulations under the Mine Health and Safety Act (Act 29 of 1996).

2.5.1 The skin notation

The history of skin notations associated with OELs can be traced back to 1958, when it was first introduced by Germany. In 1961, The American Conference of Governmental Industrial Hygienists (ACGIH) adopted the same approach (Nielsen and Grandjean, 2004). The only original intention of a skin notation was for it to be used as a qualitative warning sign, indicating that a specific substance may penetrate the human skin with the potential of contributing significantly to total systemic toxicity (Sartorelli, 2002; Nielsen and Grandjean, 2004). This implies that substances causing toxic effects such as irritancy, corrosiveness and sensitisation without skin permeation are not assigned with a skin notation (Sartorelli *et al.*, 2007).

At present skin notations are associated with almost every country's list of OELs, but assignment between countries was proven to be inconsistently different (Nielsen and Grandjean, 2004). The authors compared skin notations of five European countries (Denmark, Germany, Netherlands, Poland

and Slovenia) with that of the ACGIH. They found that agreement ranged between 24.8% (Slovenia) and 61.6% (Denmark) with a mean of 40.4%.

The reasons for differences in assignment will be discussed, but they should also be considered in light of the limitations of only having a qualitative dichotomous notation system.

Reasons for different assignment of skin notations by countries:

1. Differences in the written criteria between countries and consequentially the interpretation and use thereof (Nielsen and Grandjean, 2004). The scientific evidence required for assignment is clearly stated by some countries, but not by others. The criteria used for assignment in South Africa, Australia, Finland, Sweden, United Kingdom, British Colombia (Canada) and ACGIH (United States of America) are discussed in Chapter 7 of this thesis. For criteria of selected other countries the reader is referred to Nielsen and Grandjean (2004).

2. There is a general lack of dermal absorption data for substances (Nielsen and Grandjean, 2004; Semple, 2004). Human volunteer studies are limited by ethical considerations and direct extrapolation of animal data is not possible for various reasons (Sartorelli, 2002). As with lethal dose (LD_{50}), numerous experimental protocols exist for establishing the skin absorption of substances *in vivo* and *in vitro*.

3. Inclusion of other criteria such as LD_{50} by the ACGIH and in Poland (Kupczewska and Czerczak, 2006; ACGIH, 2009). However, the inconsistent use of LD_{50} has previously been reported (Kennedy *et al.*, 1993; Sartorelli, 2002). Furthermore, LD_{50}'s have their own limitations such as the existence of several different protocols, being species and time dependent and only reflecting acute toxicity following a single exposure (Chen *et al.*, 2003; Nielsen and Grandjean, 2004). The inclusion of other criteria is driven mainly by the lack of skin absorption data available.

4. Inclusion, although incorrectly, of substances with irritant, corrosive and sensitisation effects (Nielsen and Granjean, 2004).

5. Skin notations often do not reflect the current state of knowledge or include recommendations made for assigning new notations (Schulte *et al.*, 2009).

6. Assignment or non-assignment is not always accompanied by specific reference to supporting documentation and arguments. This lack of transparency makes it almost impossible to trace why substances were given or not given a notation, establish when it was assigned or last reviewed/revised, and is counter-productive for knowledge transfer (Nielsen and Grandjean, 2004).

The limitations and problems associated with a qualitative dichotomous skin notation can be summarised as follow:

1. It indicates the existence of a dermal risk, but is not indicative of the degree of hazard (Sartorelli, 2002).

2. It is often used as an instrument for risk management and non-assignment of a substance is not only related to the absence of a skin absorption hazard and systemic toxicity, but also to the absence of irritation and sensitisation. In most cases, non-assignment rather relates to insufficient data being available (McDougal and Boeniger, 2002; Sartorelli, 2002; Nielsen and Grandjean 2004; Sartorelli *et al.*, 2007).

3. Evidence suggests that damaged or compromised skin is far more common in occupational settings than once thought (Kezic and Nielsen, 2009). There is also increasing evidence that damaged or compromised skin enhances skin absorption of substances. This could lead to a total underestimation of skin absorption, since skin absorption data are based on penetration through uncompromised skin.

4. The skin notation is based on individual ('neat') substances, but exposure is often to mixtures of active substances and vehicles (Nielsen and Grandjean, 2004; Sartorelli *et al.*, 2007). Penetration enhancers are substances such as detergents, vehicles or solubilisers. They often do not induce systemic toxicity themselves during normal use, but enhance the skin absorption/penetration of other substances (Nielsen and Granjean, 2004).

5. Irritants, corrosive substances and allergens as skin hazards are not recognised or indicated as such (Sartorelli *et al.*, 2007).

At present, clearly defined universally accepted criteria for assignment of skin notations do not exist. Numerous scientific papers, scientific committees and commissions have proposed their own improved skin notation criteria or strategies to improve the criteria (Fiserova-Bergerova *et al.*, 1990; Kennedy *et al.*, 1993; de Cock *et al.*, 1996; Czerczak and Kupczewska, 2002; Nielsen and Grandjean, 2004; Kupczewska-Dobecka and Czerczak, 2006; Sartorelli *et al.*, 2007; Lavoue *et al.*, 2008).

The National Institute for Occupational Safety and Health (NIOSH, USA) published a new strategy for assigning skin notations in 2009 (Schulte *et al.*, 2009). Based on scientific evidence the existing 142 substances currently listed by NIOSH and other substances will be assigned with multiple or combined skin notations (where necessary) to distinguish between systemic and non-systemic effects caused by exposure (Table 2). Substances for which insufficient data associated with skin exposure exist will be identified as well as substances not posing a skin health risk. Additionally, substances that

have not been evaluated by this strategy will also be indicated. It thus aims to provide clear warnings to everybody.

Table 2: Skin notations assignment according to NIOSH (Schulte *et al.*, 2009).

Abbreviation	Explanation
$ID^{(SK)}$	After evaluation, insufficient data exist to assess the skin exposure hazard accurately
ND	Not evaluated by this strategy and the health hazard associated with skin exposure is unknown
SK	Skin notation
~~SK~~	Indicating that reviewed data did not identify a health risk associated with skin exposure
SK:DIR	Potential for direct effects to the skin following contact with a substance
SK:DIR (COR)	Potential for a substance to be corrosive following skin exposure
SK:DIR (IRR)	Potential for a substance to be a skin irritant following skin exposure
SK:SEN	Potential for immune-mediated reactions following exposure
SK:SYS	Potential for systemic toxicity following skin exposure
SK:SYS (FATAL)	Highly or extremely toxic substance and may be potentially lethal or life threatening following skin exposure

2.5.2 The sensitiser notation

Sensitisation occurs through immunologic mechanisms (refer to Section 2.1.5.2). Initially, upon exposure to a sensitiser, little or no response is observed. However, after sensitisation has occurred, subsequent exposure to the sensitiser, even at minute concentrations (even far below the OEL), a response also known as a hypersensitivity reaction may be elicited. These hypersensitivity reactions may have an immediate (e.g. asthma, rhinitis) or delayed onset (e.g. skin rash) (Schulte *et al.*, 2009).

The many reasons given for different assignment of skin notations also apply to sensitisation notations. In general, sensitisation notations refer to the potential of a substance to produce sensitisation, irrespective of the route of exposure (respiratory system, skin or conjunctiva) (ACGIH, 2009). However, countries such as the United Kingdom and South Africa (Regulations for Hazardous Chemical Substances) do acknowledge the route of exposure, but only assign notations to respiratory sensitisers (ACGIH, 2009; HSE, 2005; Department of Labour, 1995). The NIOSH sensitisation notation is assigned to substances causing or contributing to (i) allergic contact dermatitis through skin exposure, (ii) systemic allergic reactions, and (iii) immune-mediated respiratory diseases. As with a skin notation, the absence of a sensitisation notation does not necessarily imply the substance's inability to cause sensitisation, but rather points to inconclusive scientific evidence (ACGIH, 2009). The lack of human evidence is even more pronounced in skin sensitisation and allergic contact

dermatitis with reliance predominantly on predictions and animal data (Sartorelli *et al.*, 2007; Schulte *et al.*, 2009). The lack of references to supporting documentation is also highly evident.

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Chapter 3: Dermal exposure chapter in MHSC handbook

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3.1 Background

The Handbook on Mine Occupational Hygiene Measurements is a sequel to the respected handbook of the Chamber of Mines of South Africa, entitled 'Measurements in Mine Environmental Control', which was last revised and published in 1988. The handbook was produced for the Mine Health and Safety Council (MHSC) under Research Project SIM 04-09-03 by the Mine Ventilation Society of South Africa (MVS) and the Southern African Institute for Occupational Hygiene (SAIOH). The chapter on dermal exposure (Chapter 12) is one of 13 new chapters, expanding the 1988 publication.

Writing an eight page chapter on such a broad topic such as dermal exposure proved to be quite a daunting task. Yet, as authors it was decided to include the most important basic aspects of dermal exposure. Reference was also made to a number of dermal exposure publications in a bibliography in an effort to guide interested readers to more specific publications.

12. Dermal Exposure

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12.1 Purpose

Dermal exposure monitoring is conducted to assess exposure to the skin by harmful materials such as chemical, biological or radioactive substances. This Chapter provides a description of the techniques commonly used to measure dermal exposure to chemicals using dermal dosimetry.

12.2 Background

Dermal exposure can occur by direct contact with contaminants (chemical substances) through immersion or spillages, indirect contact with contaminated surfaces or clothing and deposition of contaminants directly from air.

Dermal hazards refer to chemical substances that can cause dermatitis or otherwise damage the skin, as well as to chemicals that can enter the body through the intact skin and cause other toxic effects. Use of the "skin" notation for an OEL is intended to alert the reader that air sampling alone is insufficient to quantify exposure accurately and that measures to prevent significant skin contact and/or chemical absorption may be required. The DME 2006 listing of OELs includes some 117 airborne pollutants with a skin notation.

Evaluating dermal exposure can be difficult and warning signs to the exposed individual may be limited. However, being aware of the substances in work environments and applying basic scientific principles along with some regularly used tests can be useful. Dermal exposure data can be used in the risk assessment process to help predict exposures for specific activities.

In comparison to air sampling and even biological monitoring, dermal dosimetry is not a routine procedure. Thus far its use has been limited to research and to specially-designed studies. Individuals applying dermal dosimeters should be thoroughly trained regarding the placement and retrieval of the dosimeters, as well as the recording of observations and other information about the activity. In addition to objective parameters, observed work practices can also have significant influences on dermal exposure and close observation is therefore necessary. Statistical analysis is fundamentally important in this respect[1].

A variety of measurement methods and strategies have been developed to quantify dermal exposure. These methods include: surrogate skin methods, removal of contaminant methods and fluorescent tracer methods. In addition, several risk assessment models have also been developed to estimate dermal exposures.

12.3 Legislation

Section 11 of the MHSA requires employers to "assess and respond to risk". Dermal exposure monitoring can be used to evaluate employee exposures to contamination and is useful in assessing the effectiveness of control measures, including proper work practices.

Section 12 of the MHSA requires employers to "conduct occupational hygiene measurements". Dermal exposure measurements can be deemed to be occupational hygiene measurements.

Section 13 of the MHSA requires employers to "establish a system of medical surveillance". Once excessive dermal exposure to a substance has been identified, this information should be provided to the occupational medical practitioner to address in the medical surveillance programme.

DERMAL EXPOSURE

12.4 Dermal Exposure Sampling Methods

12.4.1 Surrogate Skin Methods

These methods estimate the quantity of a contaminant deposited on the skin or clothing. Surrogate skin methods aim to collect contaminants in a manner similar to skin and include patch dosimeters, glove dosimeters and whole body dosimeters.

12.4.1.1 Patch Dosimeters

The use of dosimeter patches is arguably the most frequently used method to quantify dermal exposure. Patch dosimeters have predominantly been used to estimate dermal exposure to pesticides, but have also been used to assess exposure to copper oxide, PAHs and dusts.

The patch dosimeter method measures dermal exposure by means of absorbent patches that are attached to specified areas of a worker's body, either inside or outside the clothing. Patches of pre-determined size serve as collection media for the chemical substance to measure the amount of chemical coming into contact with the clothing or skin. After exposure, the patches are removed and analysed for chemical content. The quantities of chemical on patches from a specified location on the body are used in conjunction with standard body surface area data to estimate potential dermal exposure. Differences between chemical deposition on patches placed inside and outside of clothing can be used to determine clothing penetration factors.

(a) Composition and Size

The composition and size of the patches used in dermal dosimetry studies are important considerations and should be based on the physical-chemical characteristics of the substance and the exposure scenario. High quality alpha-cellulose will absorb a considerable amount of residue without disintegrating. Another material that is satisfactory and more readily available in small lots is preparative chromatography paper. Other appropriate materials include surgical gauze, clothing material and blotter paper.

In extremely dusty environments, investigators should consider patch materials that are porous enough to collect dusts or dried residues. Surgical gauze is suggested as an appropriate material for dry formulations. Typically, patch materials should not require pre-extraction to remove substances that interfere with sample analysis. This should be determined before beginning exposure tests using such patches. Patches should be approximately one mm thick and backed with an impermeable material such as aluminium foil, polyethylene or glassine paper. These materials will reduce the potential for contamination of the patches by materials on the skin or clothing and prevent seepage of collected residues through the patch to the skin or clothing.

Dermal patch dosimeters often consist of 8 x 8 cm or 10 x 10 cm 12-ply square sponges, backed with four to six sheets of polyethylene. Placing this sandwich in a commercially available protective aluminised paper envelope with a circular open collecting area is a convenient way to protect the dosimeter from mechanical damage and to minimise cross contamination while handling.

(b) Location and Attachment

Each patch dosimeter is a sandwich holding a passive matrix flat (like a cotton gauze sponge) to protect it from skin perspiration. Either one or two sets of patch dermal dosimeters can be used. The most important is the set placed against the skin under the clothing. Errors are likely to result when using patch dosimeters attached to the inside of clothing that are free to move relative to the skin. Dosimeters so positioned may not collect contaminants reaching the skin via penetration through openings (such as the neck, sleeves, or cuffs), nor be affected as much by the air movement carrying contaminant through the weave of the fabric.

If the determination of actual penetration of work clothing is desired in the field study, additional patches can be attached to workers' outer garments. Care must be taken to ensure that any patches attached to the outer clothing are near, but do not cover patches under the clothing.

Some examples for attaching the dosimeters are given below.

- One approach for dermal dosimeters worn under normal work clothes is to pre-attach those for the torso and upper arms to a tight-fitting T-shirt; those for the lower arms and legs to a pre-attached elastic band with a Velcro release; and, as an alternative, those for the legs may be attached to leg chaps (special leggings).
- Dosimeters worn over normal work clothes are pre-attached to a 3.8 cm open net smock covering the chest, back, upper arms, and upper legs; those placed on the head, lower arms, lower legs may be pinned or attached via duct tape to the wearer's clothing.
- The dermal dosimeters are to be put in place before exposure begins and must remain in place throughout the duration of exposure.

Patches should be attached, according to the exposure situation, to collect residues representative of those depositing on all regions of the body. Normally, a complete set for each exposure period will consist of 10 to 12 patches. Patches should be attached under test subjects' clothing on the skin or to the inner clothing. Patches should be attached at the following locations: top of the shoulders, back of the neck just below the lower edge of the collar, the upper chest near the jugular notch, back of the forearms and front of the thighs and lower legs. Inside patches must be centred under seams as well as under un-seamed material, because seams are often the areas of maximum penetration.

Where workers are engaged in some activity that is likely to result in extraordinary exposure to regions of the body that are not well-represented by the usual patch locations, extra patches must be included to assess such exposure.

Patches may be attached to the skin using material such as surgical tape, which will hold the patches during vigorous activities. Patches may be attached to clothing using safety pins, staples or tape.

Some investigators use specially-designed harnesses or lightweight vests fitted with open-fronted pockets to hold the shoulders, chest, and back patches. These alternative attachment methods have been used successfully and are acceptable. The patches should be evaluated for potential contamination or losses from or to adhesives or holders [2].

(c) Removal and Handling

The procedure for handling exposed patches will depend on the stability of the chemical(s) being studied. If the pre-field study results indicate that the chemical is stable on moist exposure patches, then the patch should be placed in a pre-labelled protective bag or envelope in a manner that avoids both cross-contamination with its holder and residue loss from contact with the bag or envelope. All bags or envelopes containing exposed patches from one exposure of a single test subject should be grouped together. Care should be taken not to contaminate the patches in handling. If the pre-field study results indicate that the chemical is unstable, the investigator needs to provide a suitable method for handling the patches that is documented prior to the study.

(d) Storage

Samples should be stored in a manner that will minimise deterioration and loss of collected chemicals between collection and analysis. The study investigator is responsible for demonstrating the stability of the samples under the storage duration and conditions used.

12.4.1.2 Glove Dosimeters

Thin cotton gloves are worn on the hands or over other personal protective gloves during a work shift, thereafter the gloves are removed for analysis. The whole glove or sections of the glove are analysed for contaminants. This method has several disadvantages, which include tearing of the gloves, which may impair work and create hazards as well as being prone to saturation by liquid contaminants, thereby overestimating exposure to liquids. Furthermore, analysis of the whole glove may require large volumes of acid for digestion, thereby making it expensive.

12.4.1.3 Whole-body Dosimeters

Whole-body dosimeters are typically sets of long cotton underwear (a one-piece set is sometimes called a union suit) that minimises the effect of non-uniform deposition on a body part. They suffer from the lack of a protective barrier between the skin and dosimeter and may add heat stress to the wearer. After use, a whole-body dosimeter may be dissected into portions covering individual body parts for analysis. As with gloves, analysis of the complete suit may be expensive [3].

12.4.2 Removal of Contaminant Methods

Contaminants deposited on the skin can be removed by wiping, washing/ rinsing [4], tape-stripping of the skin [5] or by making use of other specialised approaches such as suction devices [6]. The amount of contaminant that is removed represents the amount of contaminant present on the skin at the time of sampling. Due to low capital costs and ease of use, these methods have frequently been used, in particular to assess dermal exposure to pesticides. These methods are most suited to contaminants of low volatility and which remain on the skin surface for a significant period of time. Retention and recovery efficiency studies are conducted in laboratories or other controlled environments. Retention efficiency studies evaluate the ability of the removal medium (wipes, tape strips etc.) to retain the contaminant, while recovery efficiency studies evaluate the efficiency of removal of the contaminant from surfaces or the skin of volunteers.

Techniques and media for wipe-sampling of skin contamination vary with the agent and purpose of the sample. It is important to appreciate that there are concerns related to direct wipe-sampling of the skin, including the possibility of promoting skin absorption with the use of certain solvents.

Before any skin wipe is taken, explain to the particular worker why you wish to sample his/ her skin and ask the worker about possible skin allergies to the chemicals in the sampling medium or wetting solution. Workers may elect not to allow sampling of their skin. As an alternative to direct skin sampling, an indirect measurement of skin contamination as well as PPE failure, can be assessed by wipe-sampling surfaces that workers can touch, e.g., table tops, handles, control knobs or the inside surfaces of protective equipment.

Classic wipe-sampling techniques, employing glassfibre filters, mixed cellulose ester filters, smear tabs, gauze squares or charcoal-impregnated pads, may be used for sampling contaminants on the skin. If it is deemed desirable to moisten the collecting medium to improve collection efficiency, procedures will normally utilise either de-ionised water, or a 50% solution of isopropyl alcohol in water.

Hand washes may be appropriate in some cases. Twenty millilitres of distilled or de-ionised water, or a dilute solution of mild soap, may be added to a zipper-style sandwich bag. The hand to be sampled is inserted, and the bag held tightly closed around the wrist. After a few seconds of agitation, the hand is carefully removed, and the wash solution is poured back into a scintillation vial for shipment to a laboratory.

In the tape stripping method, pieces of adhesive tape are applied for one to two minutes to exposed skin surfaces such as the hands, forearms, neck and forehead. One to two layers of the stratum corneum (outermost layer of epidermis consisting of dead corneocytes in a lipid matrix) is removed by the adhesive tape and analysed for contaminant content. As with some other dermal sampling methods, efficiency validation of the method is also required. Numerous different adhesive tapes, with a wide range of efficiencies have been used in various studies. When removal efficiency with one tape stripping is not efficient, on average two to five consecutive tape strippings are performed to enhance removal of the contaminant. In most instances these strippings are pooled together for analysis.

12.4.3 Fluorescent Tracer Methods

This method uses a fluorescent tracer [7] compound added to a specific production process. Upon exposure the fluorescent tracer and contaminants from the process are deposited on the skin. The fluorescent tracer marks the specific location of contaminant deposition on the skin. The skin is then exposed to long-wave UV light and a video camera is used to record images of the exposed parts

of the body. This method has been successfully used to quantify dermal exposure to metal-working fluids and pesticides.

12.5 Analytical Methods

Validated methods of appropriate or sufficient sensitivity are needed for all sample analyses. It is implicit in any use of dosimeters that the chemical to be assessed is stable on the matrix, that it can be efficiently extracted, and that there is no background or interference with its analysis. While such assurance should be established before sampling, field spikes prepared from spiking solutions and field blanks are usually prepared, handled and analysed at about a 1:10 ratio with field samples to assure dosimeter accuracy for the particular compound.

12.6 Data Presentation

Individual body locations and total residue data should be reported in tabular form. The residues should be reported as µg or mg of chemical per surface area (i.e., normalised to patch sample surface area: µg/cm² or mg/cm²). Distribution data should be provided where possible.

12.7 Data Acquisition and Analysis

After dosimeters have been in place throughout an activity involving exposure, they are carefully prepared for extraction (the quantitative removal of the chemical from the collection matrix) and analysed for the mass of chemical. The resulting measured levels of contaminant can be used in several ways. Most of the following calculations would apply equally well to pads placed either outside of clothing or inside. Various calculations can be made to determine the deposited chemical (mg) and perhaps the dose density (µg/cm²) and the dose rate (mg/h).

The first example is to calculate the dermal deposition density. To do this, the total mass of contaminant found during analysis is divided by the surface area of the pad(s), at each body location.

$$\textit{Dermal deposition density } (\mu g/cm^2) = \textit{Chemical mass/Dosimeter area}$$

To calculate someone's total dermal deposition, it is necessary to assume that the deposition density on the local body part is accurately represented by the deposition density measured on the dosimeter. A set of standard body surface areas is typically used. Such an assumption allows the local dermal deposition to be calculated as follows:

$$\textit{Dermal deposition (mg)} = \textit{Chemical mass} \ (\textit{Anatomic area/Dosimeter area})$$

The validity of this assumption can be judged based on observation of the dermal exposure situation. A semi-quantitative judgement can be made by comparing the proportion of dose measured at each location among different users performing nominally similar tasks. Some variation is expected in both the distribution and total dermal deposition at all the locations.

If dosimeters were only placed outside the clothing, the "potential dose" that may have penetrated the worker's clothing can only be inferred. The inter-location distribution of the dermal dose will allow one to interpret the impact of hypothetical changes in work practices or protective clothing on the user's total dose.

One additional step is to compare the dermal dose to the inhalation dose. This comparison can include adjustment factors for both dermal adsorption and/or respiratory retention.

As with all other approaches to assessing dermal exposures, there are limitations to their use. Among the most important of these limitations is the difficulty in collecting actual deposits of volatile chemicals. An alternative type of pad has been designed to retain a high fraction of volatile chemicals, either agricultural or industrial in origin, but adjusting dermal measurements for ambient vapours complicates its use.

A summary of the dermal evaluation procedure is given in Figure 12.1.

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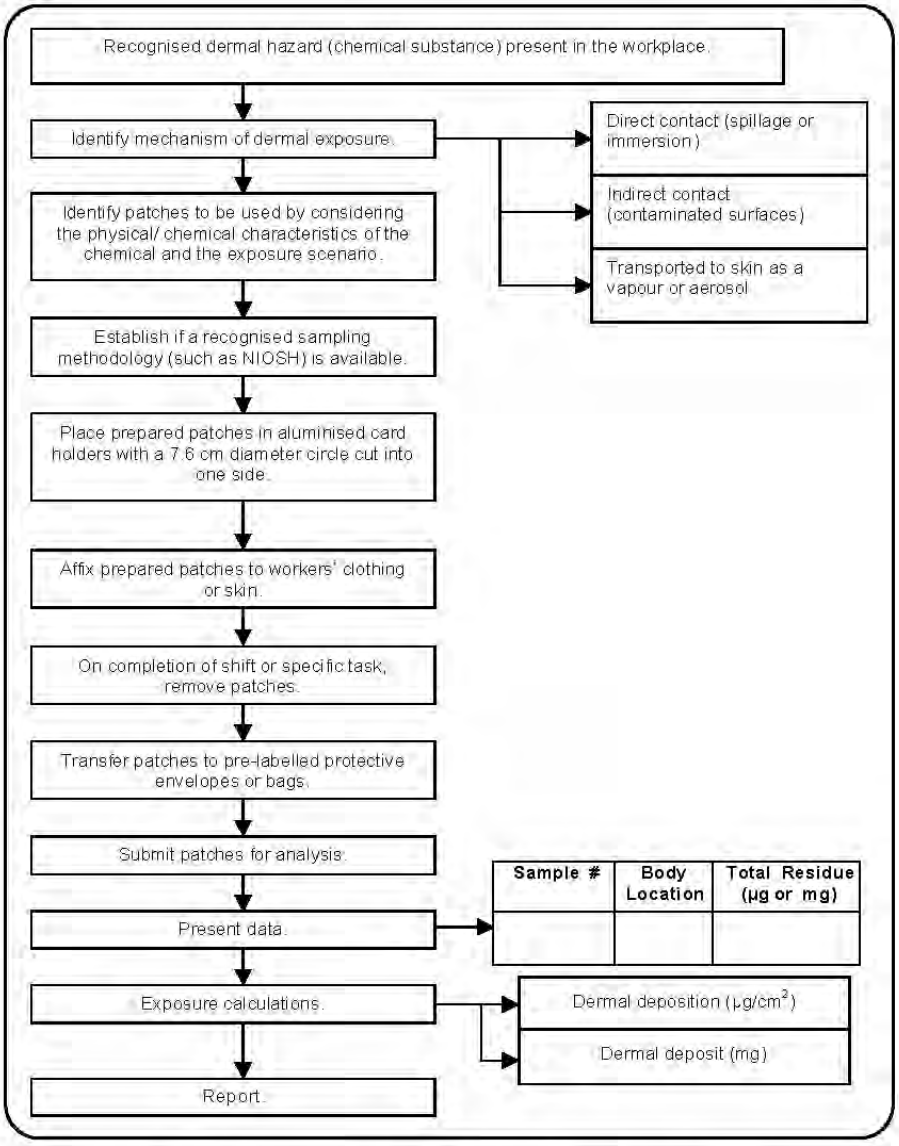

Figure 12.1 Summary of the Dermal Evaluation Procedure

12.8 Example of Sampling for Chlorinated or Organonitrogen Herbicides (Agricultural Pesticide) - NIOSH Analytical Method 9201

12.8.1 Equipment and Sampling

- Dermal patch (such as shown in Figure 12.2)
  (Polyurethane foam (PUF) pads, 10 x 10 cm, 3 to 4 mm thick)
- Passive exposure
  Place patch in an aluminised card holder with 7.6 cm diameter circle cut in one side. Affix to worker's clothing or skin.

Figure 12.2 SKC Dermal PUF Patch in Surgical-grade Aluminised Holder (left) and SKC Individual Dermal PUF Patch (right)

The SKC PUF patches are specially cleaned squares available in a medical-grade aluminised holder or individually for attachment to clothing or skin for the sampling of herbicides according to NIOSH Method 9201.

12.8.2 Analysis

- After sampling, transfer patches to 120 mL wide-mouthed glass jars with PTFE-lined caps
- Desorb each patch with 40 mL isopropanol
- Analyse by gas chromatography using an electron capture detector

12.8.3 Reports

During application, a Field Investigator should record information on:

- the site, its location, indoors or out, amount of product used, type of equipment used;
- the environment, temperature, humidity, air velocity and direction with respect to applicator and work, exposure time;
- the clothing worn, work clothing (coveralls, jacket, hat or cap, etc.) and protective clothing (gloves, goggles, face shield, respirator, etc.); and
- any occurrence of visible skin wetting or saturation and the surfaces and approximate areas involved.

This information must also be contained within the report.

Individual body locations and total residue data should be reported in tabular form in the results section of the report. The residues should be reported as µg or mg of chemical per surface area basis (i.e., normalised to patch sample surface area: µg/cm^2 or mg/cm^2). Distributional data should be provided, to the extent possible.

All the dermal survey findings must be recorded (see Chapter 2 Report Writing).

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Chapter 4: Article I

Du Plessis JL, Eloff FC, Badenhorst CJ, Booysen R, van Aarde MN, Laubscher PJ. (2008) Dermal exposure sampling methods: An overview. Occup Health SA; 14(July/August): 4-11.

4.1 Background

When the chapter on Dermal exposure was written for the MHSC Handbook (previous chapter), it became apparent that due to the number of pages (space) allocated to this broad topic, only a limited amount of information could be included. Furthermore, the above mentioned handbook is also aimed at those primarily involved in Occupational Hygiene in the South African mining industry. It was, therefore, decided to elaborate in more detail on the different dermal sampling methods in a review article sent to the journal, *Occupational Health Southern Africa*, the official journal of the South African Society of Occupational Health Nursing Practitioners (SASOHN, the South African Society of Occupational Medicine (SASOM), the Southern African Institute for Occupational Hygiene (SAIOH) and the Mining Medical and other Health Care Professionals Association (MMOA).

4.2 Instructions to authors (excerpt)

Articles reporting original and relevant research are welcomed. Review articles must contribute to the body of knowledge, and not just repeat previously documented findings. The articles should not exceed 2500 words, and use the following format:

Title: This should reflect the contents of the manuscript, without being overly long. *Abstract:* Include an abstract of less than 150 words. *Introduction:* This should clearly indicate the nature of data gathering, the main issues to be covered, definition and delimitation of the problem, the importance of the paper and the purpose of the research or review. The date when the research was conducted must be provided. The cited literature (which may be part of the introduction or a separate section) must be relevant and correctly acknowledged. *Methodology:* The research methodology employed must be clearly described and justified. For quantitative analyses the statistical tests must be relevant and appropriately interpreted. Where appropriate, evidence of ethical clearance must be provided (the name of the organisation and an ethics clearance number). *Results:* These must be accurate, comprehensive and relate to the purpose of the research or review. *Discussion:* The findings should be discussed in the light of the literature and indicate how the paper has contributed to the body of knowledge. *Conclusions and recommendations:* Conclusions must relate to the findings, whilst recommendations should be logical and feasible.

References: All articles should be appropriately referenced. References should be set out in the Vancouver style according to the International Committee of Medical Journal Editors, available at http://www.nlm.nih.gov/bsd/uniform_requirements.html. Only approved abbreviations of journal titles should be used. References should be inserted in the text as superscript numbers and listed at the end of the article in numerical order (not alphabetically). The accuracy of references is the author's responsibility. Personal communication and unpublished observations may be cited in the text, but not in the reference list.

Manuscript: Manuscripts should be typed in 1,5 spacing, using only one side of the paper. The font used for the body of the article should be Arial 11pt. All captions should be in Times New Roman 12pt. Pages should be numbered consecutively and leave wide margins (3,17 cm left and right, 2,54 cm top and bottom). Scientific measurements should be expressed in S.I. units. Abbreviations and acronyms should only be used if absolutely necessary and must be defined on first use. Illustrations, tables and graphs should be submitted separate to text, in electronic format. Photographs (preferably without identifying details of patients) must be submitted as images of at least 300 dpi. Please ensure that they are not embedded in MS Word documents. All these accompanying materials should be clearly identified by means of captions that are also indicated in the text of the manuscript. Tables should use Arabic numerals, 1, 2, 3, etc, and illustrations Figure 1, 2, 3, etc. Additional material can be supplied as complementary data that will form part of the electronic journal.

Author's details: A separate title page should contain the title, the author(s)' full names, contact details relevant to correspondence and the author(s)' position in a public sector department and/or affiliation to an academic institution (if relevant). Authors who are members of MMOA, SAIOH, SASOHN or SASOM must indicate this membership. A word count should be included on this page.

PEER REVIEWED

Dermal exposure sampling methods: An overview

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Abstract

Although a total of 174 and 117 substances have been listed with a skin (Sk) notation in the Regulations for Hazardous Chemical Substances and Regulation 22.9 of the Mine Health and Safety Act respectively, dermal sampling is not used frequently to assess exposure to these substances. A variety of measurement methods and strategies have been developed during the past forty years to assess dermal exposure. These methods include interception methods (also referred to as surrogate skin methods), removal of contaminant (substance) methods and *in situ* detection methods (also referred to as fluorescent tracer methods). The aim of this paper is to give an overview of the different dermal sampling methods. Furthermore, the applicability of each method for sampling different hazardous chemical substances will be highlighted in order to assist Occupational Hygienists in choosing the correct dermal sampling method.

Introduction

Exposure to hazardous chemical substances occurs primarily through inhalation, ingestion or skin contact. With a few exceptions Occupational Hygiene has traditionally focused on inhalation exposure because it is generally considered to be the most important route of exposure.[1] Furthermore, until the mid-1960s, the skin was incorrectly considered as an almost impermeable barrier for chemicals. Since then, skin absorption has been demonstrated for a number of hazardous occupational and environmental chemical substances.[2]

The Regulations for Hazardous Chemical Substances lists 174 substances and Regulation 22.9 of the Mine Health and Safety Act lists 117 substances with a skin (Sk) notation. This Sk notation refers to a substance's ability to penetrate the intact skin and thus being absorbed into the body. However, dermal sampling in comparison to air sampling and biological monitoring is not used frequently.

Dermal exposure normally occurs by one of three pathways, namely direct contact with contaminants (substances) through immersion or spillages, indirect contact with contaminated surfaces or clothing and deposition of contaminants directly from air.[1,3,4]

To date, a variety of measurement methods have been developed to assess dermal exposure. These methods can be grouped into three categories, namely (i) surrogate skin methods, (ii) removal of contaminant methods and (iii) fluorescent tracer methods.[3,5-7] More recently, the use of 'interception methods' as replacement terminology for 'surrogate skin methods' and '*in situ* detection methods' as replacement terminology for 'fluorescent tracer methods' has been introduced.[8]

The aim of this paper is to give an overview of the different dermal sampling methods. Furthermore, the applicability of each method for sampling different hazardous chemical substances will be highlighted in order to assist occupational hygienists in choosing the correct dermal sampling method.

Wipe sampling of the hand

1. Interception methods (surrogate skin methods)

Interception methods estimate the amount of a contaminant that is deposited on the skin or clothing. This is accomplished by placement of a collection medium on the

" Interception methods ... measure the potential exposure to a contaminant"

skin or clothing that is capable of collecting and retaining a contaminant in a manner similar to skin, which can then be analysed after extraction from the collection medium. Therefore, these methods measure the potential exposure to a contaminant and include patches, gloves and whole body suits as collection media.[3,7,9]

1.1 Patch sampling

A patch dosimeter is arguably one of the most frequently used dermal sampling methods, in particular to quantify skin exposure to pesticides.[7,10] It has also been used to quantify skin exposure to chromium, copper oxide, metal working fluid, polyaromatic hydrocarbons and dusts.[7,11-16] Several organisations such as the World Health Organization (WHO), Environmental Protection Agency (EPA) and Organization for Economic Co-operaration and Development (OECD) have established "standard" methods for patch sampling.

The type of material used as patches is primarily determined by the contaminant to be collected and the environment in which sampling is conducted. Alpha-cellulose paper has been used as patches to assess skin exposure to pesticides, metal working fluid and chromium.[7,11-13] Polypropylene pads have been used as patches to assess exposure to polyaromatic hydrocarbons, while charcoal cloth may be used to assess exposure to volatile compounds. For dusts and other dry particulate matter, porous patches constructed with layers of surgical gauze are recommended. Other materials used include cotton, polyester/cotton, rayon/polyester, dracon/cotton, flannel, filter paper, filter paper impregnated with lanolin and polyurethane foam pads. Patches are generally backed with a waterproof material such as aluminium foil or polyethylene in order to prevent contamination of the patches by contaminants on the skin/clothing and to prevent collected contaminants from moving through the patch onto the skin.[7]

Several different sizes of patches have been used. The most common size used is 10 x 10 cm (100 cm^2). Smaller sizes have also been used, but this is not recommended. Larger patches may be used for body parts with a large surface area (such as the back or chest).[7]

The number of patches used per worker differ between methods and range from a minimum of six suggested by the WHO and 13 suggested by the OECD. These patches are placed on body parts where possible exposure is expected. The most common positions are on the top of the head, on top of the shoulders, on the back of the neck just below the lower edge of the collar, on the upper chest close to the jugular notch or on the sternum, on the back between the shoulder blades, on the left and right upper arm, on the left and right forearm (midway between wrist and elbow), on the left and right upper leg and on the left and right lower leg.[7,10-13] Patches may also be attached underneath clothing to determine possible contaminant penetration through clothing. Patches are attached to the different body parts with safety pins, staples, skin tapes, clothing tapes or open net smocks, which are now commercially available.

After use, patches must be removed and stored separately from other patches in such a way as to minimise contaminant loss prior to analysis. Exposure is obtained from the product of the mass of contaminant collected on

the patch and the ratio of the patch area to the body part area.[7]

The major limitation of this method is that it only estimates the amount of contaminant deposited on a particular surface area. An assumption is also made that contamination is uniformly distributed, which might not always be the case. The patch (or patches) represents only a small proportion of the total body surface area and therefore could lead to an under- or overestimation of exposure.[7] In certain cases this could be overcome by using larger patches. Furthermore, in reality the adherence of contaminants to patches and human skin differs, which could also lead to estimation errors. It is therefore important to establish the ability of patches to capture (absorb) and retain a contaminant. This is done through conducting retention and recovery efficiency studies in laboratories or other controlled environments prior to field sampling. The aim of a retention efficiency study is to evaluate the ability of the collection material (e.g. an alpha-cellulose patch) to retain a contaminant, while a recovery efficiency study evaluates the efficiency of removal of the contaminant from the collection material for analysis.[3,7] Advantages of this method include its ease of use and lower cost of analysis when compared to other surrogate skin methods.[7]

1.2 Cotton glove sampling

Thin cotton gloves may be used to assess dermal exposure to low levels of exposure to viscous low volatility liquids and pesticides.[9,17] These gloves are worn on the hands or over other personal protective gloves during a work shift, whereafter the gloves are removed for analysis. The whole glove (or sections) of the glove is analysed for contaminants. This method has several limitations which include tearing of the gloves, which may impair work and create hazards as well as being prone to saturation by liquid contaminants, thereby overestimating exposure to liquids.[9,12,17] Furthermore, analysis of the whole glove requires large volumes of acid for digestion,[18] making it expensive.

Dermal sampling measurement system to measure the hydration level of the skin. The lower the value, the drier the skin. Cracked and damaged skin may influence absorption of HCS through skin

1.3 Whole body suit sampling (whole body dosimetry)

Whole body dosimeters are typically sets of lightweight, cotton or cotton/polyester mix overalls/underwear that cover the body, arms and legs. Exposure to the head can be measured by attachment of a hood or hat, while exposure to the hands and feet can be measured by using gloves and socks, respectively.[7] To date, their use has been confined to assess pesticide exposure. The main advantage of this method is that no assumptions relating to the uniform distribution of contaminants have to be made when compared to patches.[3] After use, a whole-body dosimeter may be dissected into portions covering individual body parts for separate analysis.[7,19] As with gloves, analysis of the complete suit is expensive.[7] Limitations of this method include susceptibility of suits to breakthrough, the possibility of the worker experiencing heat stress and as with gloves, expensive analysis due to the large volumes of acid required.[3,7]

1.4 Biological dermal sampler

Recently a prototype IOM (Institute of Occupational Medicine) dermal sampler was developed to mimic uptake of contaminants through the skin. It consisted of an adsorbent sandwiched between a permeable membrane and an impervious backing. The concentration of contaminant on the membrane surface may be estimated from the mass collected on the adsorbent and the known permeation rate through the membrane. The sampler gave reproducible results in laboratory and field trials, but the adsorbent became rapidly saturated and the mean permeation rate of membrane was much higher than the permeation rate through skin. The future use and success of this method is dependent on finding a less permeable membrane, which has characteristics closely resembling human skin.[7,20]

2. Removal of contaminant methods

Contaminants can be removed from the skin by wiping, washing/rinsing, tape stripping of the skin or by making use of specialised removal devices. The amount of contaminant that is removed represents the actual amount of contaminant present on the skin at the time of sampling (actual exposure).[5,9] Due to the low costs of sampling materials, analysis thereof and ease of use, these methods

" 174 and 117 substances have been listed with a Sk notation, yet dermal sampling is not performed frequently."

have frequently been used to assess dermal exposure to pesticides.[3,5] All of these removal methods are most suited to low volatility contaminants and to contaminants which remain on the skin surface for a significant period of time. However, it is important to establish the ability of sampling materials and devices in removing contaminants from the skin. This is done through conducting retention and recovery efficiency studies as described in section 1.1.

2.1 Skin wipe sampling

The wipe sampling of skin method is similar to or adapted from general surface sampling methods published by OSHA and US EPA.[5] Similar to hand washing, contaminants are removed from the skin by a combination of mechanical forces and wet chemical action. As with surfaces in general, the skin is not a smooth surface and may have imperfections such as furrows, whorls, scars and calluses that will most likely influence removal of contaminants.[21] Hand wipes are less effective in removing contaminants from the skin when compared with hand wash sampling.[22] Skin wipe sampling has been successfully used and validated to quantify exposures to pesticides, polyaromatic hydrocarbons, isocyanates, nickel, lead, zinc and antimony trioxide.[9,23,24]

A wide variety of sampling or collection media have been used and some are commercially available. They differ in terms of type, surface size and the presence or absence of wetting liquids in the sampling medium. Cellulose, cotton fabric, filter paper (Whatman 542 or 41), nonwoven polyester fabric, cotton balls, sponges, cellulose smear tabs and 12-ply cotton surgical pads have been used as sampling media.[5,24] For isocyanates, wipes are impregnated with polypropylene glycol in order to improve recovery of unbound isocyanates from the skin surface.[23] The size of the collection media (4,8 – 25 cm^2) varies according to the type used.[5,21] Dry collection media is considered to be less efficient than wet or moist collection media.[21] Soaked or wetted (moist) sampling media have also been used in skin wipes sampling. Wetting liquids used include deionised water, ethanol, isopropanol, polyethylene glycol and soap.[5] A wetting liquid should be carefully selected so as not to be an irritant to skin, which may be detrimental to the barrier function of the skin.

In general, skin wipe sampling is limited to the hands (palms, fingertips), forearms, forehead and neck.[5,18] The operator must wear gloves that need to be changed after sampling a specific position, in order to prevent contamination of the wipe used. With the exception of the hands, templates are used to indicate the sampling area for other skin surfaces.[5] The surface area depends on the body part and circular, square or rectangular templates have been used. Several different sizes of disposable or reusable templates are also commercially available. The number of passes made with one wipe over a sampling area varies and is dependent on the removal efficiency of the wipe. In some instances more than one wipe (up to six) is performed and pooled together for analysis. It has also been reported that the amount of pressure applied by the operator might influence the efficiency of the method. Where possible, one operator should perform all skin wipes to prevent or reduce inter-operator variability.[25]

2.2 Tape strip sampling

This quantitative, minimally invasive method has been widely used in dermatology and has been approved by the US Federal Drug Administration as part of a standard method to evaluate topical dermatological dosage forms.[26] To date, this method has been used for dermal and/or surface sampling of acrylates, asbestos fibres, diisocyanates, glass fibres, jet fuel, pesticides, wood resin acids, toxic metals, and fungi in controlled laboratory studies making use of volunteers and in workplaces.[5,25-37] After exposure, pieces of adhesive tape are applied for one to two minutes to exposed skin surfaces such as the hands, forearms, neck and forehead. One to two layers of the stratum corneum (outermost layer of epidermis consisting of dead corneocytes in a lipid matrix) are removed by the adhesive tape and analysed for contaminant content.[5,26,28,29,33,36] As with some other methods, efficiency validation of the method is also required. Numerous different adhesive tapes, with a wide range of efficiencies have been used in various studies. When the removal efficiency with one tape stripping is not efficient, on average two to five consecutive tape strippings are performed to enhance removal of the contaminant. In most instances these strippings are pooled together for analysis.[33]

2.3 Skin wash sampling

Contaminants are removed from the skin by providing an external force that is equal to or exceeds the force of adhesion to the skin. Skin wash sampling is primarily used to remove contaminants from the hands of exposed workers. Three methods, namely hand washing, hand rinsing and finger immersion sampling can be identified.[5] Due to similarities, hand washing and rinsing will be discussed under one heading.

Wipe sampling of the skin, in this instance only the finger

2.3.1 Hand washing/rinsing methods

This method has primarily been used to quantify dermal exposure to pesticides.[17,38,39] The hands of exposed workers are immersed into a bag, bowl or bottle (volume of 250 – 500 ml) containing a washing/rinsing liquid for a predetermined time. With hand washing, the skin is scrubbed by mechanical agitation caused by the movements and pressure of both hands in a washing liquid in a routine washing fashion. The contaminant is removed from the skin by a combination of mechanical forces and wet chemical action (dissolution). Hand rinsing involves pouring of washing liquid over the hands and removal of contaminants by a combination of hydrodynamic drag and dissolution, without using any mechanical force. With the bag-rinsing method specifically, the hand is immersed in rinsing liquid and should be shaken for a fixed number of shakes, a fixed time or a fixed number of shakes in a fixed time to facilitate removal of contaminants. Afterwards, extracts from the washing/rinsing liquid are transferred to a sample tube for analysis. Tap water, distilled or deionised water, water in combination with commercial surfactants, liquid hypoallergenic hand soaps, ethanol and 10% isopropyl alcohol have been used as washing/rinsing liquids.[5,38] Sampling efficiency tests are necessary to validate the method prior to field work. This could be done through a mass-balance method for non-liquid contaminants or direct spiking method for liquid contaminants.[3,5] Reported sampling efficiencies range from unacceptably low to very high levels and it is evident that the type of washing/rinsing liquid influences efficiency. Furthermore, the use of solvents as washing/rinsing liquid may disrupt the barrier function of the skin, thereby enhancing skin absorption of contaminants. In general, it is difficult to interpret skin wash results in terms of contaminant mass per surface area.[5]

2.3.2 Finger immersion sampling

An adaptation of the above-mentioned methods involve immersion of only the thumbs and index fingers of exposed workers directly into sample tubes containing ultra pure water. Although results are limited, this method shows advantages over wipe testing and tape stripping in terms of extraction efficiency, speed and ease of use in the field.[22]

2.4 Suction methods

Suction sampling has been widely used for more than three decades to assess particulate contamination on surfaces such as floors, but their use for dermal exposure assessment has been limited.[40] Suction samplers

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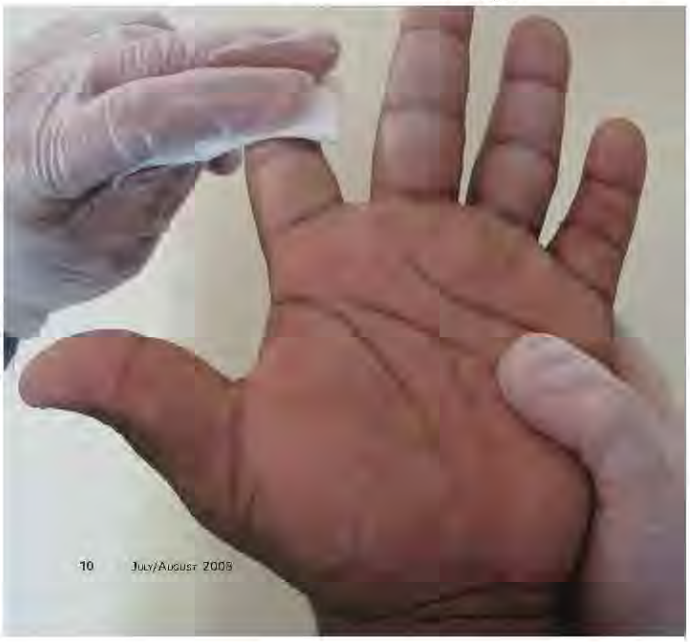
can be divided into vacuum samplers and Smair samplers.

A vacuum sampler is a pump that draws air through a nozzle held on a surface, including the skin. Suction action generates a combination of lift and drag forces that removes particulates when adhesion force between deposited material and the surface is exceeded. Particulates are collected on a 37 mm, 0,8 µm membrane filter or Whatman filter paper. In both suction and Smair samplers, the sampled area is controlled by the dimension of the sampling nozzle and is varied by moving the nozzle from one location to another. A suction sampler can have a wide range of dimensions, but to be effective it must be recognised that the dimensions and the suction flow rate are interdependent. The angle between the vacuum sampler nozzle and the sampled surface was found to influence sampling efficiency. For one such sampler, the optimum angle was found to be 45°.[40]

Smair samplers employ air impingement to redisperse loose contamination from surfaces and dispersed particulates are collected on a membrane filter. A Smair sampler is similar to conventional air samplers with the open end placed against a surface. The air intake is restricted by a series of small holes drilled at angles so as to direct jets of air onto the surface to be sampled.[25]

Both types of samplers enable collection of particulates from large areas and subsequent analysis thereof. Unfortunately, the removal efficiency of vacuum samplers and Smair samplers from skin is very low, relative to other sampling methods such as wiping, but evaluations have been limited to a few studies.[25,40] In comparison with other methods, suction sampling is also more expensive.

Wipe sampling of the skin, in this instance only the finger



3. *In situ* detection method (Fluorescent tracer method)

This method was successfully used to quantify dermal exposure to metal working fluids and pesticides.[6,13,41,42] A fluorescent tracer is added to a specific production process and exposure due to this process will lead to deposition of the contaminant and fluorescent tracer on the skin and/or clothing.[3] The specific location of skin deposition is thus marked by the fluorescent tracer which can be visualised with long-wave UV light and recorded by a video camera. By digitising the analogue camera signal an image consisting of pixels with a 0-256 value (grey level) is generated. The grey levels of before and after exposure are then compared to obtain a decrease in grey level. The relationship between the amount of tracer and grey scale is established and the mass of contaminant deposited on the skin can then be estimated.[42] Used quantitatively this method also provides information on the pattern of contaminant emissions from a source to surfaces and may be the only way to identify and quantify secondary sources of contamination. This method may provide improved accuracy in dermal exposure assessments, since it measures actual skin loading levels and requires no distributional assumptions to be made. It can also identify previously unrecognised exposure pathways and is valuable for worker education and training, because exposure and the patterns thereof can be visualised.[6]

The method requires the introduction of a foreign substance, the fluorescent tracer, into the production system. In many instances, except for agricultural settings, tracer addition to a source is impossible or impracticable. Potential tracer degradation due to sunlight also needs to be evaluated. Implementing the method also involves very high costs which were estimated to be in the order of several hundred thousand rand in 2006.[6]

Conclusions

Dermal sampling is not conducted as frequently as air sampling, partly due to the fact that inhalation as a route of exposure is generally considered to be more important than the skin.[1] Therefore, dermal exposure data from occupational settings is quite scarce and exposure models have often been used in the past as an alternative in risk assessment. Furthermore, dermal exposure sampling is currently a mixture of different methods and relatively few examples of standardisation thereof exist. This makes a comparison of data almost impossible. Some organisations such as the International Council on Mining and Metals, Eurometaux and Eurofer, recently proposed the use of wipe sampling for dermal exposure monitoring of metals in an effort to standardise and validate data in the future.[9] Finally, the potential to conduct dermal exposure monitoring in the southern African industrial and mining sectors is vast and hopefully this review will stimulate the use of dermal exposure sampling as a monitoring strategy.

" The in situ detection method ... may be the only way to identify and quantify secondary sources of contamination."

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Chapter 5: Article II

Du Plessis JL, Eloff FC, Badenhorst CJ, Olivier J, Laubscher PJ, van Aarde MN, Franken A. (2010) Assessment of dermal exposure and skin condition of workers exposed to nickel at a South African base metal refinery. Ann Occup Hyg; 54:23-30.

5.1 Background

Assessment of airborne exposure to nickel at the electro-winning plant (tank house) of the base metal refinery is conducted frequently. However, a few cases of sensitisation to nickel in recent years prompted Occupational Hygienists at the base metal refinery to assess the potential dermal exposure to nickel. After dermal exposure to nickel was confirmed through collection of a few 'crude' samples, a more elaborate project was planned, which incorporated assessment of worker's skin condition (skin hydration and TEWL) and assessment of potential contamination of workplace surfaces.

5.2 Instructions to authors (excerpt)

Annals of Occupational Hygiene publishes material that significantly extends knowledge on any aspect of occupational health and hygiene.

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

Authorship: The corresponding author should be identified in the submission. Full postal addresses must be given for all co-authors. The preferred practice is that persons should only be named as authors if they have made significant identifiable intellectual contributions to the work, and other contributions may be recognised by acknowledgement at the end of the submission, in accordance with the guidance issued by the International Committee of Medical Journal Editors. A letter consenting to publication should be signed by all authors of a submission and sent to the Editorial Office.

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

Conflicts of interest: The source of financial support for the work must be stated in the Acknowledgements, unless it is clear from the authors' affiliations. Other conflicts of interest must be declared to the Editor at the time of submission. These may include financial interest in products described, including stock or share ownership, and payment for consultancy or legal testimony using the material in the paper.

Language: Manuscripts must be in English. British or American styles and spelling may be used, but should be used consistently, and words or phrases which might be unclear in other parts of the world should be avoided.

Brevity, and supplementary material: The necessary length of a paper depends on the subject, but any submission must be as brief as possible consistent with clarity. The number of words, excluding the abstract, references, tables and figures, must be stated as a message to the Editor at the time of submission. If this length is more than 5000 words, a statement must be included justifying the extra length, and papers without this information may be returned unread. It is possible to include supplementary material, such as large data sets, in the on-line edition only, and authors are encouraged to take advantage of this. This material must be included in the submission, but not in the word count.

Structure: Papers should generally conform to the pattern: Introduction, Methods, Results, Discussion and Conclusions - consult a recent issue for style of headings. A paper must be prefaced by an abstract of the argument and findings, which may be arranged under the headings Objectives, Methods, Results, and Conclusions. Keywords should be given after the list of authors.

Survey design: Sampling surveys should be planned using modern statistical principles so that the quality of the data is good enough to justify the inferences and conclusions drawn.

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

Figures: Good quality low resolution electronic copies of figures, which include photographs, diagrams and charts, should be sent with the first submission. It is helpful to reviewers to incorporate them in the word-processor text or at the end. The revised version, after refereeing, should be accompanied by high-resolution electronic copies in a form and of a quality suitable for reproduction. They should be about the size they are to be reproduced, with font size at least 6 point, using the standard Adobe set of fonts. Fine hairlines should be avoided and clear hatching patterns should be used in preference to solid grey shadings wherever possible. They should be on separate pages at the end of the text.

Tables: Tables should be numbered consecutively and given a suitable caption, and each table typed on a separate page. Footnotes to tables should be typed below the table and should be referred to by superscript lowercase letters.

References: References should only be included which are essential to the development of an argument or hypothesis, or which describe methods for which the original account is too long to be reproduced. Only publications which can be obtained by the reader should be referenced. References in the text should be in the form Jones (1995), or Jones and Brown (1995), or Jones et al. (1995) if there are more than two authors. For example: Jones and Brown (1995) observed total breakdown of control... or Total breakdown of control has sometimes been observed (Jones and Brown, 1995).

At the end of the paper, references should be listed in alphabetical order by name of first author, using the Vancouver Style of abbreviation and punctuation. Examples are given below. ISBNs should be given for books and other publications where appropriate. Material unobtainable by readers should not be cited. Personal Communications, if essential, should be cited in the text in the form (Professor S.M. Rappaport, University of California). References will not be checked editorially, and their accuracy is the responsibility of authors.

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Assessment of Dermal Exposure and Skin Condition of Workers Exposed to Nickel at a South African Base Metal Refinery

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Objectives: The objectives of this study were to assess dermal exposure of cell workers to nickel at a South African base metal refinery and to characterize their skin condition by measuring the skin hydration and trans epidermal water loss (TEWL) indices. Methods: The skin hydration index of the index finger, palm, neck, and forehead was measured before, during and at the end of the shift. The TEWL index was measured before and at the end of 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. Neck and forehead samples were collected before and at the end of the shift. Wipe samples of various surfaces in the workplace were also collected. Wipes were analyzed for nickel according to NIOSH method 9102, using inductively coupled plasma-atomic emission spectrometry. Results: Hydration indices measured on the hands decreased significantly during the shift, but recovered to normal levels by the end of the shift. TEWL indices for the index finger and palm of the hands are indicative of a low barrier function even before commencement of the shift, which further deteriorated significantly during the shift. During the shift, substantial nickel skin loading occurred on the index finger and palm of the hand. Levels on the neck and forehead were much lower. Various workplace surfaces, which workers come into contact with, were also contaminated with nickel. Conclusions: The skin condition and high levels of nickel on the skin were most probably caused by inadequate chemical protection provided by protective gloves. Although, the permeability of nickel through intact skin is considered to be low, a decreased barrier function of dehydrated or slightly damaged skin will increase its permeability for nickel. The ethnicity of these exposed workers may contribute significantly toward the low incidence of allergic contact dermatitis observed. Several measures to lower dermal exposure to nickel are also recommended.

Keywords: dermal exposure; nickel; refinery; skin condition

INTRODUCTION

Occupationally as well as among the general population, nickel is considered to be the most common contact allergen causing type IV (delayed) hypersensitivity reactions. Sensitization occurs generally after direct and prolonged skin contact with nickel ions (Vahter *et al.*, 2007). Following dermal or systemic exposure, nickel-allergic contact dermatitis manifests in a wide range of skin eruptions (Hostynek, 2002, 2006).

Occupational hygiene has traditionally focused on inhalation exposure because it was generally considered to be the most important route of exposure. This

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meant that other exposure routes, such as ingestion and dermal absorption, were often overlooked (Sartorelli, 2002; Semple, 2004). There are three types of chemical–skin interactions. First, the chemical may become systemic after passing through the skin. Second, the chemical may act locally, thereby causing effects such as irritation, burns, or degradation of the skin barrier function. Third, the chemical may induce allergic skin reactions. However, in all three instances, diffusion of the chemical through the outer skin layers is a prerequisite (Semple, 2004).

The skin is a complex membrane and the percutaneous absorption of metals through human skin is governed by several interrelated mechanisms and influenced by numerous exogenous and endogenous factors (Hostynek, 2002). The *in vitro* permeation rate for nickel through intact skin is considered to be very low, yet *in vivo* it elicits allergic skin reactions on contact in sensitized individuals (Hostynek, 2003). Recently, Larese Filon *et al.* (2007) reported an *in vitro* permeation flux of 0.0165 $\mu g\ cm^{-2}\ h^{-1}$, a permeability coefficient (K_p) of 6.1×10^{-4} and a very long lag time of 14.56 h. Results also indicate that *in vivo*, nickel ions may permeate simultaneously by routes of diffusion such as the shunt pathway and the slower transcellular/intracellular diffusion pathway (Tanajo *et al.*, 2001).

Numerous measurement methods and strategies have been developed during the past 40 years to assess occupational dermal exposure. Most of these dermal exposure studies have focused on liquid contaminants such as pesticides. These methods include interception methods (surrogate skin methods), removal of contaminant (substance) methods, and *in situ* detection methods (fluorescent tracer methods) (Fenske, 1993; Brouwer *et al.*, 2000; Cherrie *et al.*, 2000; Soutar *et al.*, 2000; Du Plessis *et al.*, 2008). However, no dermal (skin) occupational exposure limits exist for any hazardous chemical substances.

Recently, Hughson *et al.* (2009) reported dermal and inhalation exposure to nickel in nickel production and primary user industries. Based on different tasks, dermal exposure was measured by using moist wipes to recover nickel from defined areas of the skin and analysing samples for soluble and insoluble nickel species.

To our knowledge, there is no published literature reporting the actual measurement of skin condition upon exposure and the subsequent use thereof in conjunction with dermal exposure results. Two parameters that give an indication of skin condition are the hydration index and trans epidermal water loss (TEWL) index. The skin hydration index reflects the skin's surface moisture level. TEWL reflects the total amount of water vapor lost through the skin under normal sweating conditions (Rawlings, 2006). TEWL is accepted as a reliable indicator of epidermal barrier homeostasis (Fluhr *et al.*, 2008; Rawlings *et al.*, 2008).

The objectives of this study were to assess dermal exposure of cell workers to nickel at a South African base metal refinery and to characterize the worker's skin condition by measuring skin hydration and TEWL indices.

METHODS

Workplace description

A nickel sulfate solution was pumped to the tank house (electro-winning plant) where metallic nickel was recovered from the solution using an electrolytic process. The electrolytic process transpired in 122 individual cells (electrolytic tanks) where nickel deposited onto cathodes (40 cathodes per cell). Cell workers were responsible for frequent inspections of electrodes and ensuring that the electrolytic process occurs optimally. Cathodes were removed from the cells after 6–7 days where after they were transported to an adjacent area for cutting and packaging.

Operations at the tank house are divided into three shifts, morning, afternoon, and night shift. The morning shift is considered as the shift with the highest risk of dermal exposure due to the range and extent of activities performed. It is also the shift with the most workers ($n = 59$). The afternoon and night shifts are considered as maintenance shifts with a lower risk of dermal exposure.

Twenty-six African cell workers volunteered and gave informed consent to participate in this study. Samples were collected during the morning shift of four different days. This project was approved by the Ethics Committee of the North-West University (number NWU-0026-07-S6).

Measurement of skin condition

Skin condition was measured with a EDS12 Dermal Measurement System (EnviroDerm Services, Evesham, UK) equipped with a hydration and TEWL probe. The skin hydration indices of the index finger, thumb, and palm on the ventral side of the dominant hand as well as the neck and forehead were determined before the shift, just prior to any break in shift (i.e. tea and lunch break), and at the end of the shift. For the palm of the hand, neck, and forehead, the average of at least two measurements are reported. The range and interpretation of the hydration index is indicated in Table 1.

The TEWL index was measured before and at the end of the shift on the index finger (dominant hand), palm of the hand (dominant hand), and forehead. The range and interpretation of the TEWL index is indicated in Table 2.

Skin condition questionnaire

Basic worker information such as the number of years employed in the tank house was recorded. To evaluate dermatological complaints, a validated questionnaire developed by Dalgard *et al.* (2003) was used. The questionnaire was also translated into Setswana, the native language of the participating workers. The questionnaire consists of 10 simple questions concerning common skin complaints. The answers to all the questions were scored on a four-point scale (1: no; 2: yes, a little; 3: yes, quite a lot; 4: yes, very much) and the mean was calculated. According to the authors, subject scores higher than 1.3 for non-healthcare-seeking populations have an increased risk of developing skin diseases.

Skin wipe samples

Dermal exposure samples were collected by making use of a removal method. Samples were collected before washing in order to assure that they were representative of the level of skin contamination during the shift. Commercial wipes, Ghostwipes™ (individually wrapped and moistened with distilled H_2O by the manufacturer), were used to collect samples from each worker, before the shift, prior to any break in the shift (i.e. tea break and 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 at the above-mentioned intervals. Neck and forehead samples were collected before and at the end of the shift. Index finger wipe samples were collected from the two most distal joints of the finger. The surface area was calculated by making a trace of the finger on paper. The trace and a 4-cm^2 reference area was cut out and repeatedly weighed ($n = 5$) on a scientific Sartorius balance (Sartorius, model number BP211) to determine their average mass. The surface area was calculated as follows: surface area of finger = mass of finger trace/mass of 1 cm^2. For palm, neck, and forehead samples, 10-cm^2 (4 × 2.5-cm) acetate sheet templates were used. The same operator, who wore a clean pair of disposable vinyl gloves for each sample, collected all samples. Each sample consisted of a single wipe that was wiped three consecutive times across the same sampling area. All samples were placed in separate storage vials. Twelve field blank samples were also collected. Wipes were analyzed for nickel by an accredited analytical laboratory in accordance to NIOSH method 9102, using inductively coupled plasma-atomic emission spectrometry. The minimum level of detection for this method was 0.01 μg cm^{-2} nickel. Skin loading was expressed as micrograms nickel per square centimeter.

Table 1. Range and interpretation of hydration index measurements

Hydration index	Skin condition
1	Extremely dry
2	Very dry
3	Dry
4	Slightly dry
5–8	Normal
9–12	Excessively hydrated

Table 2. Range and interpretation of TEWL index measurements

TEWL index	Skin barrier function	Skin condition
0–4	Excellent	Very healthy
5–9	Good	Healthy
10–12	Normal	Normal
13–16	Low	Strained
17–20	Very low	Critical

Surface wipe sampling

Surfaces likely to come in contact with workers on a daily basis in the tank house tea room, smoke room, and change house were also selected for wipe sampling. For flat surfaces, a disposable cardboard template was used to demarcate a 100-cm^2 (10 × 10-cm) area. Each sample consisted of a single Ghostwipes™ that was used to wipe the area in an overlapping s-pattern. Each surface was wiped three times consecutively, each time the exposed side of the wipe was folded inward. For uneven surfaces, such as door handles, the surface area was also wiped three times, but without using a template. The same operator collected all samples and wore a clean pair of vinyl gloves for each sample. Samples were stored and analyzed the same way as skin wipe samples. Where applicable, results were expressed as micrograms nickel per square centimeter, otherwise only as micrograms nickel per sample.

Statistical analysis

All results were statistically analyzed using Statistica Version 8.0 (Statsoft Inc., 2009). TEWL indices, hydration indices, and wipe results were compared

for statistical significance with paired Student's *t*-tests or repeated measures analyses of variance (ANOVAs) with a Bonferroni post-hoc test. Wipe data were not normally distributed and therefore log-transformed for statistical analysis. Interday variation of results was determined with ANOVAs. A Pearson correlation was done to correlate the nickel loading between different anatomical sites. A linear regression analysis was performed to correlate skin condition with years of employment. All results with a $P < 0.05$ were considered to be statistically significant.

RESULTS

Cell workers participating in this study ($n = 26$) worked in the tank house for an average of 7.96 ± 6.51 years (minimum: 1 year; maximum: 24 years). The workers wore a two-piece acid repellent overall and a disposable FFP2 face mask for respiratory protection. Due to the risk of cuts, up to three types of gloves were worn at one time, namely a cotton liner (toweling) glove (product code: GLKW), silver talon whizard glove (product code: 134527), and a flock lined latex glove (commarex 8", product code: GCOM20). Not all workers preferred to wear the liner glove underneath the whizard glove. Whizard gloves were replaced when damaged, while new liner and lined latex gloves were worn at the start of each shift.

Mean hydration indices decreased significantly from normal, for the thumb (Fig. 1B) and slightly dry for the index finger (Fig. 1A) and palm (Fig. 1C), to between dry and very dry during Break 2. By the end of the shift, all the mean hydration indices recovered (increased) to levels similar to those measured before the shift. Hydration indices for the neck and forehead were normal before the shift and by the end of the shift they were even higher, indicating an improvement in the hydration levels thereof.

The mean TEWL index (Table 3) for the forehead before the shift is considered to be normal. The mean TEWL indices for both the index finger and the palm of the hand had a low barrier function, indicating a strained skin condition, even before the shift commenced. At the end of the shift the mean forehead TEWL index drastically deteriorated to a low barrier

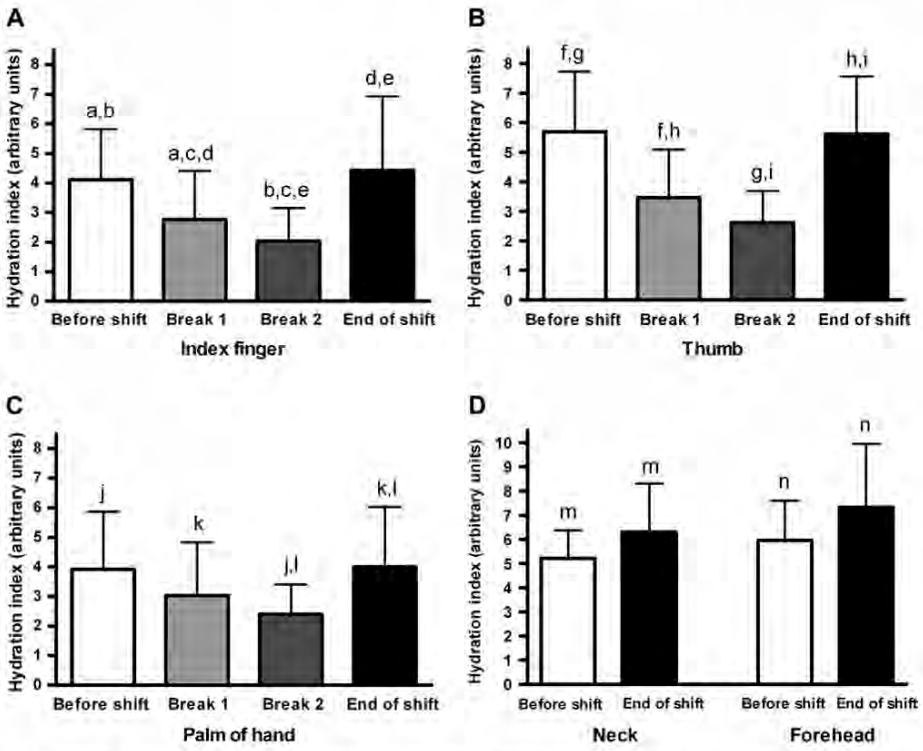

Fig. 1. Hydration index for the (A) index finger, (B) thumb, (C) palm of the hand, and (D) neck and forehead ($n = 26$). a–n indicates statistical significance ($P < 0.05$) between means. Statistical significance was determined by repeated measures ANOVA with a Bonferroni post-hoc test for (A), (B), and (C), while a dependent Student's *t*-test was used for (D).

function (indicative of a strained skin condition), while the TEWL indices for the index finger and palm of the hand deteriorated even further to very low barrier function which is indicative of critical skin condition. For all three anatomical sites, the increase of the mean TEWL index between the start of the shift and end of the shift was highly statistically significant (index finger: $P = 0.003$; palm of hand: $P = 0.01$; forehead: $P < 0.001$).

A total of 11 workers reported one or more of the following skin conditions: itchy skin (23.08% or six workers); dry/sore rash and scaly skin (both, 11.54% or three workers); pimples and warts (7.69% each or two workers); and itchy rash on hands, other rashes on the face, and troublesome sweating (3.85% each or one worker). Of those workers who reported a skin condition, six indicated that these conditions started >6 months ago. The average Dalgard skin score for all the workers was 1.112 ± 0.197 and in total, only three workers had a Dalgard score >1.3 which is indicative of being at risk of developing skin diseases. There is also no correlation between skin condition of workers and the number of years of employment in the tank house ($P = 0.825$, $r = 0.045$, $r^2 = 0.002$).

Dermal exposure data are presented in Table 4. It is evident that workers had detectible levels of nickel on their index finger, palm of the hand, neck, and forehead, even before commencement of the shift. Hand exposures were highly variable, ranging from 0.236 to 177.772 μg cm^{-2} and from 0.045 to 229.860 μg cm^{-2} measured for the index finger and palm of the hand, respectively. The geometric means of dermal exposure measured throughout the shift, for both the index finger and the palm of the hands, were relatively constant and did not differ significantly from each other. During the shift, there was also loading of nickel on the skin of the neck and forehead. However, only the amount of nickel deposited on the neck differed statistically between the start and the end of the shift. A Pearson correlation was done to determine the correlation between the amount of skin loading on the index finger, palm of the hand, forehead, and neck. The only significant correlation that existed was between the index finger and palm of the hand ($r = 0.9$, $P < 0.001$). Statistical analysis with ANOVAs proved that there was no statistical significant interday variability between skin wipe results (results not shown).

Nickel was detected on surfaces that workers are likely to come in contact with on a daily basis. On uneven surfaces, such as door handles and taps, the amount of nickel varied between 3.879 and 794.739 μg, with an average of 270.535 μg cm^{-2} ($n = 5$) and 25.733 μg cm^{-2} ($n = 7$) for each, respectively. On table surfaces ($n = 3$), the average amount was 0.308 ± 0.196 μg Ni cm^{-2}. The amount of nickel collected from the change house overall collection counter averaged 1.021 ± 0.414 μg cm^{-2} ($n = 4$), while on benches used by workers to undress and dress, the average was 0.211 ± 0.062 μg cm^{-2} ($n = 3$).

Table 3. TEWL index for the index finger, palm of the hand, and forehead ($n = 26$)

		TEWL index (arbitrary units)		
		Mean	SD	Range
Index finger	Before shift	15.538[a]	4.510	5–20
	End of shift	17.769[a]	2.717	11–20
Palm of hand	Before shift	15.115[b]	5.080	2–20
	End of shift	17.500[b]	4.022	3–20
Forehead	Before shift	10.269[c]	5.265	4–20
	End of shift	15.077[c]	5.528	5–20

SD, standard deviation.
a, b, and c indicates statistical significant differences between the means as indicated by dependent Student's *t*-tests.

DISCUSSION

Hydration indices of the index finger and palm of the hand indicated a slightly dry skin at the start and at the end of the shift, while that of the thumb was normal. Furthermore, TEWL indices indicated decreased barrier function of the skin, which was also highlighted by the occurrence of the maximum value for the index (20 arbitrary units) for each anatomical site even before the start of the shift.

Although workers wore up to three different types of gloves while performing their tasks, the decrease in the hydration index of the hands (index finger, thumb, and palm) during the shift is probably due to direct contact with the nickel–electrolyte solution (containing sulfuric acid, pH = 3.5) due to the lack of chemical protection provided by the gloves (Pavlides, 2008). The presence of sulfuric acid mist in the tank house may also contribute to this. The recovery of the hydration indices between Break 2 and the end of shift may be attributed to a very short duration of this part of the shift (<90 min), lower task activity, and some workers removing their protective gloves upon completion of all tasks. From observation, it was quite clear that the initial part of the shift (start of shift to Break 2) was far more labor intensive, where workers loaded new nickel starter sheets and inspected or removed existing sheets once they have been extracted from the cells.

Contrary to physical measurement results of the skin, the Dalgard score, based on the questionnaire,

Table 4. Nickel deposited on the skin as shown by wipe sampling and analysis by inductively coupled plasma-atomic emission spectrometry

		μg Ni cm^{-2}			
		GM	GSD	Minimum	Maximum
Index finger	Before shift	0.782[a,b,c]	2.344	0.239	2.612
	Break 1	3.709[a]	170.159	0.236	177.772
	Break 2	3.931[b]	25.349	0.301	42.339
	End of shift	2.888[c]	7.470	0.813	11.3688
Palm of hand	Before shift	0.407[d,e,f]	1.138	0.078	6.963
	Break 1	2.749[d]	94.737	0.045	229.860
	Break 2	2.936[e]	28.419	0.064	56.709
	End of shift	3.389[f]	9.699	0.517	19.439
Neck	Before shift	0.189[g]	1.039	0.034	1.169
	End of shift	1.047[g]	4.009	0.174	16.969
Forehead	Before shift	0.372[h]	1.259	0.087	8.599
	End of shift	0.893[h]	2.679	0.056	3.151

a–f indicates statistical significant differences of log-transformed data as determined by repeated measures ANOVA with a Bonferroni post-hoc test. g and h indicates statistical significance as determined by dependent Student's *t*-test. GM = geometric mean, GSD = geometric standard deviation.

indicated a normal skin condition for 88.5% of the workers. This implies that workers are of the opinion that their skin condition is healthy or pose no risk. Skin condition is also not related to the number of years employed in the tank house. The low incidence of skin conditions, such as contact dermatitis, in these African workers may be due to ethnic differences in skin structure and function, where stratum corneum function is reported to be stronger in subjects with darker skin upon chemical or mechanical challenge (Rawlings, 2006). Although reports on the incidence of allergic contact dermatitis in blacks are conflicting (Berardesca and Maibach, 2003), Dogliotti (1970) reported lower incidences in black South Africans.

The efficiency of Ghostwipes™ as sampling media in removing metals from surfaces was previously reported in the Occupational Safety and Health Administration's Method ID-125G (OSHA, 2002). The analytical recovery of nickel by means of liquid spiking was reported as 101.4%, while the removal efficiency of nickel from glass surfaces was >90%. The method's reproducibility between different persons collecting samples also provided recovery efficiencies ranging between 92.6 and 93.3%. The difference between sampling from human skin and a glass surface is acknowledged by the authors of this paper, but the same is also true for any other surrogate skin surface (i.e. cured leather or silicone rubber membranes) used in validation studies by other authors. This remains a limitation in all dermal exposure studies lacking *in vivo* validation of the method and results should be interpreted accordingly.

Recently, Hughson *et al.* (2009) reported background levels of nickel on the skin of non-occupationally exposed individuals with a geometric mean of 0.02 μg Ni cm^{-2} for the hands (ventral and dorsal sides combined). The presence of much higher levels of nickel on the skin of workers before the start of the shift in this study may have been due to the following reasons: (i) From surface sampling results, it is evident that surfaces in the change house itself (i.e. benches and overall collection counter) were contaminated. (ii) On arrival at the base metal refinery, workers dressed in their overalls in the change house, where after they proceeded to the tea room of the tank house for a briefing session before commencement of their daily tasks. In order to access the tea room, workers had to walk through the tank house itself and opened the tea room door manually. Surface wipe results indicated that this door handles and other surfaces in the tea room were contaminated. Both these reasons may explain the presence of nickel on the finger and palm of the hand, but it does not explain the detectible levels of nickel on the neck and forehead. The 'clean' (washed) overalls may also have been a possible source of contamination and handling it may significantly contribute to contamination. The interior harness of worker's hard hats that keeps the hard hat in place on the head may also have been a potential source of contamination as these are not decontaminated after completion of a shift. The possibility of significant 'take-home' contamination from previous days' exposure cannot be ruled out and future sampling before entering the change house

at the beginning of the shift and after washing up at the end of the shift will most likely clarify this matter.

Results of this study cannot be compared directly with the results of Hughson *et al.* (2009) as there are differences in the sampling protocol and anatomical sites from which samples were collected. Hughson *et al.* (2009) used a commercial wet wipe (Jeyes 'Sticky Fingers' Wet Ones) and each sample consisted of three individual wipes, each used to wipe the demarcated skin surface three times. Hand sample results reported by Hughson *et al.* (2009) represent both the dorsal and the ventral surfaces of the hands, and face samples refer to those collected from perioral (in the vicinity of the mouth) areas. Hand and forearm dermal exposure reported by Hughson *et al.* (2009) had a geometric mean of 0.56 μg cm^{-2} (total nickel) and a range of 0.16–3.19 μg cm^{-2}. The geometric mean total nickel dermal exposure was 0.25 μg cm^{-2} (<0.02 to 2.21 μg cm^{-2}) and 0.58 μg cm^{-2} (<0.02 to 4.32 μg cm^{-2}) for the neck and face (perioral), respectively. Results of our study also indicated that dermal exposure between workers was highly variable. Samples of this study were only collected from the ventral surfaces of the index finger and palm of the hand. Hypothetically, if it is assumed that exposure of the ventral surface of the index finger and back of the hand was zero, the geometric mean exposure during the shift of this study, irrespective of the difference in the sampling protocol, still proved to be 5.40–6.27 times higher than those reported by Hughson *et al.* (2009). The high levels of nickel on the hands of cell workers in this study was most probably due to inadequate chemical protection provided by the gloves used. When neck wipe results are compared, the result of our study is 4.19 times higher than those reported by Hughson *et al.* (2009).

From skin wipe results of this study, it was indicated that nickel exposure and dermal loading of the index finger and palm of the hand did not differ statistically from each other. This indicates that either the index finger or the palm of the hand may be chosen to represent the hand as anatomical sites for future dermal sampling in this occupational setting.

The amount of nickel on surfaces in the tea room, which is supposed to be a clean area, suitable for consuming food and drink, is alarming. Nickel on door handles, taps, and table surfaces therefore may potentially come into contact with unprotected skin and contribute toward the total skin loading of the shift or even be ingested.

The high levels of nickel collected from the overall collection counter of the change house is expected as this counter is right beside the bin in which workers place their contaminated overalls after completion of a shift. However, workers only hand in their contaminated overalls after taking a shower and getting dressed in civilian clothes. By handling the contaminated overall, worker's hands become contaminated with nickel and they thus leave the refinery contaminated with nickel.

Sensitization to nickel and the subsequent development to allergic contact dermatitis require direct and prolonged contact with nickel ions (Vahter *et al.*, 2007). Semple (2004) indicated that the presence of another chemical on the skin, which irritates the skin, greatly enhances permeation of the other chemical. Turkall *et al.* (2003) also found that the potential health risk from dermal exposure to nickel is enhanced if another chemical is present. Nielsen *et al.* (2007) demonstrated that limited damage to the skin significantly increases the permeability coefficient (K_p) as well as the total percutaneous penetration of chemicals, in particular those with low penetration rates through intact skin. *In vitro* experiments conducted by Larese Filon *et al.* (2009) showed an 84.87-fold increase in nickel powder's skin permeation through damaged skin when compared to healthy skin. Furthermore, Semple (2004) found that occlusion of the skin (by i.e. protective gloves) may facilitate permeation of a chemical already present on the skin, by as much as 5-fold (Semple, 2004).

From a pure economic perspective (i.e. monthly income) it seems plausible that skin care is not a very high priority for this group of workers, especially when they are of the opinion that their skin condition is healthy. This can in part explain the low hydration levels and poor barrier function observed in this study. However, they are exposed daily to an electrolyte solution with a very low pH that irritate the skin and degrade the barrier function even further (as indicated by the hydration and TEWL results) due to the inadequate chemical protection provided by the types of protective gloves used. They are also exposed to various surfaces in the workplace contaminated with nickel. Although, the permeability of nickel through intact skin is considered to be low, the decreased barrier function of dehydrated or slightly damaged skin will increase its permeability for nickel, thereby increasing the internal dose. From literature, it is also clear that occlusion provided by protective gloves may also enhance permeation. The presence of such high levels on the skin of the hands also increases the risk of oral ingestion of nickel through a hand-to-mouth shunt. However, the ethnicity of these exposed cell workers may be a significant contributor toward the low incidence of allergic contact dermatitis observed.

CONCLUSIONS

The skin on the hands of cell workers in the tank house was dehydrated and has a low barrier function probably due to frequent contact with an acidic electrolyte solution. High levels of nickel were detected on the index finger and palm of the hands. The skin condition and high levels of nickel on the skin are most probably caused by inadequate chemical protection provided by protective gloves (types selected for mechanical protection). Nickel was also detected on surfaces in the tea room and change house. Although, the permeability of nickel through intact skin is considered to be low, the decreased barrier function of dehydrated or slightly damaged skin will increase its permeability for nickel. The ethnicity of the exposed workers in this study may have contributed significantly toward the low incidence of allergic contact dermatitis. Recommended measures to lower dermal exposure were as follows: (i) selection of a combination of protective gloves that will provide mechanical and chemical protection, (ii) improvement of hand wash facilities in the tank house, (iii) changes in operating procedures for cleaning of areas and surfaces, (iv) the use of a colorimetric test (dimethylglyoxime and ammonium hydroxide) to be used as spot-checks on cleaned surfaces, (v) the use of emollient skin moisturizing cream after completion of the shift in order to improve skin condition, and (vi) more frequent information and training sessions focusing on personal hygiene.

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Chapter 6: Article III

Du Plessis JL, Eloff FC. (2010) Assessment of dermal exposure and skin condition of workers co-exposed to cobalt and nickel at a South African base metal refinery. To be submitted to Ann Occup Hyg.

6.1 Background

Results of the nickel dermal exposure study (Chapter 5) prompted a similar study at the cobalt plant of a second base metal refinery. Differences in the sampling strategy between the two studies/articles are highlighted in the following text.

Skin condition measurements differed from the sampling strategy of Article II. Workers took only one break ("lunch break") during the shift and, therefore, sampling was reduced to three intervals (before, middle and end of shift). Hydration indices were measured on the back of the hand and wrist instead of the index finger and neck (Article II). TEWL was measured during the shift as well, and not only before and at the end of the shift. A skin pH meter was acquired after completion of Article II and skin surface pH measurements were included in Article III.

The dermal exposure sampling strategy differed from Article II with regard to the sampling intervals, anatomical areas sampled and the number of consecutive wipes per sample. Sampling was done before, in the middle and end of shift. The highly significant correlation between index finger and palm of the hand exposure in Article II ($r = 0.90$, $P < 0.005$) as well as anatomical areas selected by other authors prompted the inclusion of the back of the hand at the expense of the index finger. The wrist as an anatomical area with higher risk of exposure was included at the expense of the neck. A removal efficiency of above 90% from glass surfaces was reported for the wipe technique used in Article II with each area wiped three consecutive times. After careful consideration it was decided that each area on each worker should be wiped four consecutive times in order to maintain and obtain as high efficiency as possible without handling the wipe in a manner that could compromise a sample.

6.2 Instructions to authors (excerpt)

Refer to Chapter 5 for the journal, Annals of Occupational Hygiene's instructions to authors. For the sake of readability the Figures and Tables are placed in the text. With submission the Figures and Tables will be inserted on separate pages at the end of the article as per instructions of the journal.

ASSESSMENT OF DERMAL EXPOSURE AND SKIN CONDITION OF WORKERS CO-EXPOSED TO COBALT AND NICKEL AT A SOUTH AFRICAN BASE METAL REFINERY

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4691 words (excluding abstract and references)

ABSTRACT

Objectives: The objectives of this study were to assess dermal co-exposure of refinery workers to cobalt and nickel at a cobalt plant of a South African base metal refinery and to concurrently characterise their skin condition by measuring the skin hydration index, Trans Epidermal Water Loss (TEWL) index and skin surface pH. *Methods:* The skin hydration index, TEWL index and skin surface pH of the hands (palm and back of the hand), wrist and forehead were measured before, during and at the end of the shift. Dermal exposure samples were collected with Ghostwipes™ from the dominant hand (palm and back of the hand), before, during and at the end of the shift. Wrist and forehead samples were collected before and at the end of the shift. Wipe samples of various surfaces in the workplace were also collected. Wipes were analysed for cobalt and nickel according to NIOSH method 9102, using Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). *Results:* Skin hydration indices for the hands and wrist, before and during the shift indicated various degrees of skin dryness and possible impaired barrier function. TEWL indices for the palm of the hand represented strained barrier function before and during the shift. Skin surface pH for all anatomical areas sampled decreased significantly during the shift, but remained in normal range. Cobalt and nickel were collected from the skin even before the start of the shift. Highly variable skin loading of the two metals occurred during the shift on all anatomical areas sampled. Furthermore, dermal exposure to nickel was consistently higher than that of cobalt for all anatomical areas and intervals sampled. *Conclusions:* Slightly damaged, compromised skin may lead to increased skin permeation and absorption of cobalt and nickel already present in high levels on the skin and thus increase the risk of developing allergic contact dermatitis. The risk is further increased by the co-exposure to nickel and cobalt. Despite the skin condition and high levels of dermal exposure reported, the incidence of allergic contact dermatitis at the base metal refinery is very low. Ethnic differences in skin structure and function may decrease the likelihood of African workers developing allergic contact dermatitis.

INTRODUCTION

Cobalt and nickel are important skin sensitisers, with nickel considered to be the most common contact allergen in the general population and in occupational settings (Thyssen and Menné, 2010). Concurrent allergy to nickel and cobalt may occur and it is most likely due to co-sensitisation rather than cross-reactivity (Lidén and Wahlberg, 1994; Walhberg and Lidén, 2000).

Respiratory exposure of workers involved in the production (mining and refining) of metals and metal inorganic compounds, including nickel and cobalt is well documented. In contrast, only a limited number of dermal exposure studies for metals and their inorganic compounds exist. Assessment of dermal exposure to nickel and cobalt is limited to a few studies, where exposure of carpenters, cashiers, locksmiths and workers involved in the production of cemented-carbides, gas turbines and space propulsion components were reported (Lidén *et al.*, 2008; Day *et al.*, 2009; Julander *et al.*, 2010). Only recently, Du Plessis *et al.* (2010) and Hughson *et al.* (2010) reported dermal exposure to nickel at nickel production (refineries) and primary user industries. However, there are no published data on dermal exposure to cobalt during production at refineries.

The skin acts as a physical barrier preventing loss of body fluids and penetration of chemical substances or infectious agents (Zhai and Maibach, 2002; Agache, 2004; Proksch *et al.*, 2008). This physical permeability barrier resides primarily in the stratum corneum (Pirot and Falson, 2004; Bouwstra and Ponec, 2006; Feingold, 2007). Skin hydration and transepidermal water loss (TEWL) are two parameters commonly used to assess skin condition. Skin hydration reflects the skin's surface moisture level, while TEWL represents the total amount of water vapour lost through the skin under normal sweating conditions (Rawlings, 2006), and has been used extensively to evaluate skin barrier function (Zhai and Maibach, 2002; Pirot and Falson, 2004; Levin and Maibach, 2005; Rawlings *et al.*, 2008). Du Plessis *et al.* (2010) measured skin hydration and TEWL indices of refinery workers exposed to nickel and found a decrease in skin hydration and deterioration of skin barrier function during the shift. The skin surface pH and maintenance of an optimal pH is considered to be an important regulator of the formation of the skin barrier (Agache, 2004; Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006; Feingold, 2007).

Damage to the skin, and thus a compromised skin barrier due to physical and mechanical irritation and chemical damage is suggested to be quite common in some occupational settings. Not only does compromised skin become more permeable to chemicals, but it may also facilitate absorption of irritants and allergens leading to further degradation of the skin barrier (Kezic and Nielsen, 2009). The influence of skin damage on dermal absorption of chemical substances has been studied extensively in experimental settings. Regrettably, only a limited number of workplace studies, not relevant to metals and the production thereof, have been reported. For nickel and cobalt, very limited reporting on skin

absorption through intact skin has been done (Fullerton *et al.*, 1986; Hostynek *et al.*, 2001; Tanajo *et al.*, 2001; Larese Filon *et al.*, 2004; Larese *et al.*, 2007). However, *in vitro* experiments conducted by Larese Filon *et al.* (2009) showed 84.87 and 92.90 fold increases in skin permeation through damaged (abraded) skin when compared to healthy skin for nickel and cobalt respectively. This indicates that small injuries to the skin barrier may significantly increase skin absorption.

The objectives of this study were to assess dermal exposure of refinery workers to cobalt and nickel at a cobalt plant of a South African base metal refinery and to concurrently characterise the worker's skin condition by measuring the skin hydration index, TEWL index and skin surface pH.

METHODS

Workplace description

The cobalt plant receives a mixed double salt solution containing cobalt and nickel. Through various steps involving noteworthy chemicals such as sulphuric acid and ammonia, nickel is chemically stripped from the solution to produce a cobalt sulphate solution. The cobalt sulphate solution is transferred to the cobalt-reduction area (in the same building) where it is chemically and thermally processed and dried to produce cobalt metal powder. On average, five metric tonne of cobalt powder is produced weekly.

Operations at the cobalt plant is divided into three eight hour shifts (day, afternoon and night shifts) with between two and three process operators/controllers and one laboratory analyst working per shift. The cobalt-reduction plant is only operational during the day shift.

In total, twelve workers of the cobalt plant gave informed consent to participate in the study. Two of the workers are permanently employed in the reduction area. One worker was a Caucasian (male) and the others were of African descent (10 males and 1 female). The workers held the following job-titles: process operators (n = 5), senior process operators (n = 3), process controllers (n = 3), and laboratory analyst (n = 1). One worker, a process operator, participated on two separate days. Process controllers and operators are tasked with monitoring and adjusting the processes in the respective plants, while the laboratory analyst is responsible for collecting and analysing process samples at regular intervals during the shift.

Measurement of skin condition

Skin hydration and TEWL indices were measured with an EDS12 Dermal Measurement System (EnviroDerm Services, United Kingdom) as previously reported by Du Plessis *et al.* (2010), while skin surface pH was measured with a Derma Unit SSC3 (Courage and Khazaka, Germany). All skin condition measurements were performed on the hands (palm and back of the dominant hand), wrist

and forehead before the shift, just prior to a "lunch" break (middle of the shift) and at the end of the shift. The range and interpretation of the hydration and TEWL indices is indicated in Table 1 and Table 2.

Table 1: Range and interpretation of hydration index measurements.

Hydration index	Skin condition
1	Extremely dry
2	Very dry
3	Dry
4	Slightly dry
5-8	Normal
9-12	Excessively hydrated

Table 2: Range and interpretation of TEWL index measurements.

TEWL index	Skin barrier function	Skin condition
0-4	Excellent	Very healthy
5-9	Good	Healthy
10-12	Normal	Normal
13-16	Low	Strained
17-20	Very low	Critical

Skin condition questionnaire

Dermatological complaints were evaluated by making use of a questionnaire developed by Dalgard *et al.* (2003). The interpretation thereof is described by Du Plessis *et al.* (2010).

Measurement of dermal exposure

Dermal exposure samples were collected by making use of a removal method. Samples were collected before washing in order to assure that they were representative of the level of skin contamination during the shift. Commercial wipes, Ghostwipes^{TM} (individually wrapped and moistened with distilled H_2O by the manufacturer) and 10 cm^2 (4 cm x 2.5 cm) acetate sheet templates were used to collect samples. Samples were collected from the palm and back of the dominant hand before, during (middle of shift) and at the end of the shift. Wrist and forehead samples were collected before and at the end of the shift. The same researcher, who wore a clean pair of disposable vinyl gloves for each sample, collected all samples. Each sample consisted of a single wipe that was wiped and folded four consecutive times across the same sampling area. All samples were placed in separate storage vials. Field blank samples were also collected. Wipes were analysed for cobalt and nickel by an accredited analytical laboratory in accordance to NIOSH method 9102, using Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). The minimum levels of detection for this method were 0.00087 mg Co $sample^{-1}$ and 0.0001 mg Ni $sample^{-1}$. Skin exposure was expressed as either μg Co cm^{-2} or μg Ni cm^{-2}.

Measurement of surface exposure

Several workplace surfaces in the cobalt and cobalt-reduction plant were also selected for wipe sampling. For flat surfaces, a disposable cardboard template was used to demarcate a 100 cm^2 (10 cm x 10 cm) area. Each sample consisted of a single Ghostwipe™ that was used to wipe the area three times consecutively, folding it in between, in an overlapping s-pattern. For uneven surfaces, the surface area was also wiped three times, but without using a template. Samples were collected by the same researcher and they were stored and analysed as described for skin wipe samples. Where applicable, results were expressed as μg cm^{-2}, otherwise as μg $sample^{-1}$.

Statistical analysis

Skin condition measurements and dermal exposure data were compared for statistical significance with a mixed models repeated measures procedure with a Bonferroni post-hoc test in SAS Software Version 9.1 (SAS Institute Inc., 2010). Accordingly, results are reported as estimated means ± standard error of means (SEM). Canonical correlations on log-transformed data were done in Statisitca Version 9.0 (Statsoft, Inc., 2010) to establish relationships between sets of variables [different anatomical areas, e.g. palm (all sampling intervals) vs. back of hand (all sampling intervals)] for skin condition variables. To permit the statistical use of dermal exposure data below the limit of detection (BDL), values equal to one-half of the BDL were assigned to BDL samples. Pearson correlation coefficients were obtained to evaluate possible relationships between log-transformed dermal cobalt and nickel exposures. All statistical results with a $P \leq 0.05$ were considered to be statistically significant.

RESULTS

Workplace description

Workers participating in this study have been working in the cobalt plant for at least four years. All the refinery workers wore a two-piece acid repellent overall, gloves (cotton liner glove and acid resistant PVC glove), standard safety shoes and a hard hat. Ambient temperatures ranged between 21 and 23 ºC, while relative humidity ranged between 40 and 43% during skin condition measurements.

Skin condition

Before the start of the shift, the mean skin hydration indices were below normal (range of 5 to 8) for the palm of the hand, back of the hand and wrist. For the palm (Fig. 1A), the mean skin hydration index was between very dry and dry (before shift) and stayed dry for the duration of the shift. The mean hydration index of the back of the hand (Fig. 1B) deteriorated significantly from dry (start of shift) to very dry by the end of the shift ($p = 0.003$), while for the wrist (Fig. 1C) it was between dry and slightly dry for the duration of the shift. Despite the increase in the mean forehead hydration

index (Fig. 1D) during the shift, all means were within the normal skin hydration range throughout the shift.

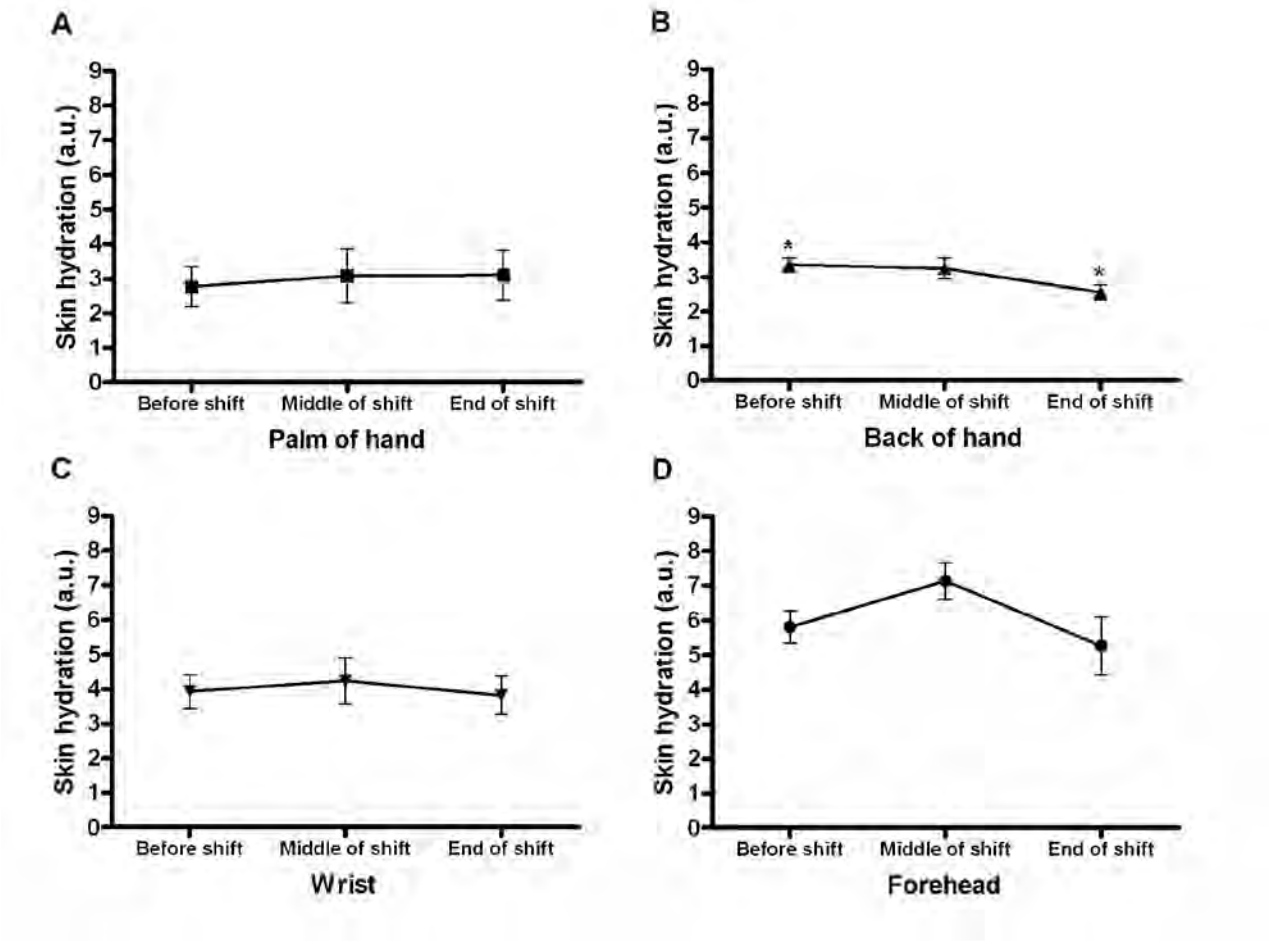

Fig. 1. Skin hydration index (estimated mean ± SEM) for the (A) palm of the hand, (B) back of hand, (C) wrist and (D) forehead (n = 13). * indicates statistical significant difference between the means and a.u. is arbitrary units.

Low skin barrier function, as depicted by TEWL indices in Fig. 2A, was measured for the palm of the hand before (13.54 ± 1.33), during (14.45 ± 1.05) and at the end of the shift (13.30 ± 1.53). Mean TEWL indices of the back of the hand (Fig. 2B) and forehead (Fig. 2C) increased from the beginning to the end of the shift, although not significantly. The skin barrier function deteriorated slightly from good, before and during the shift to normal skin condition at the end of the shift.

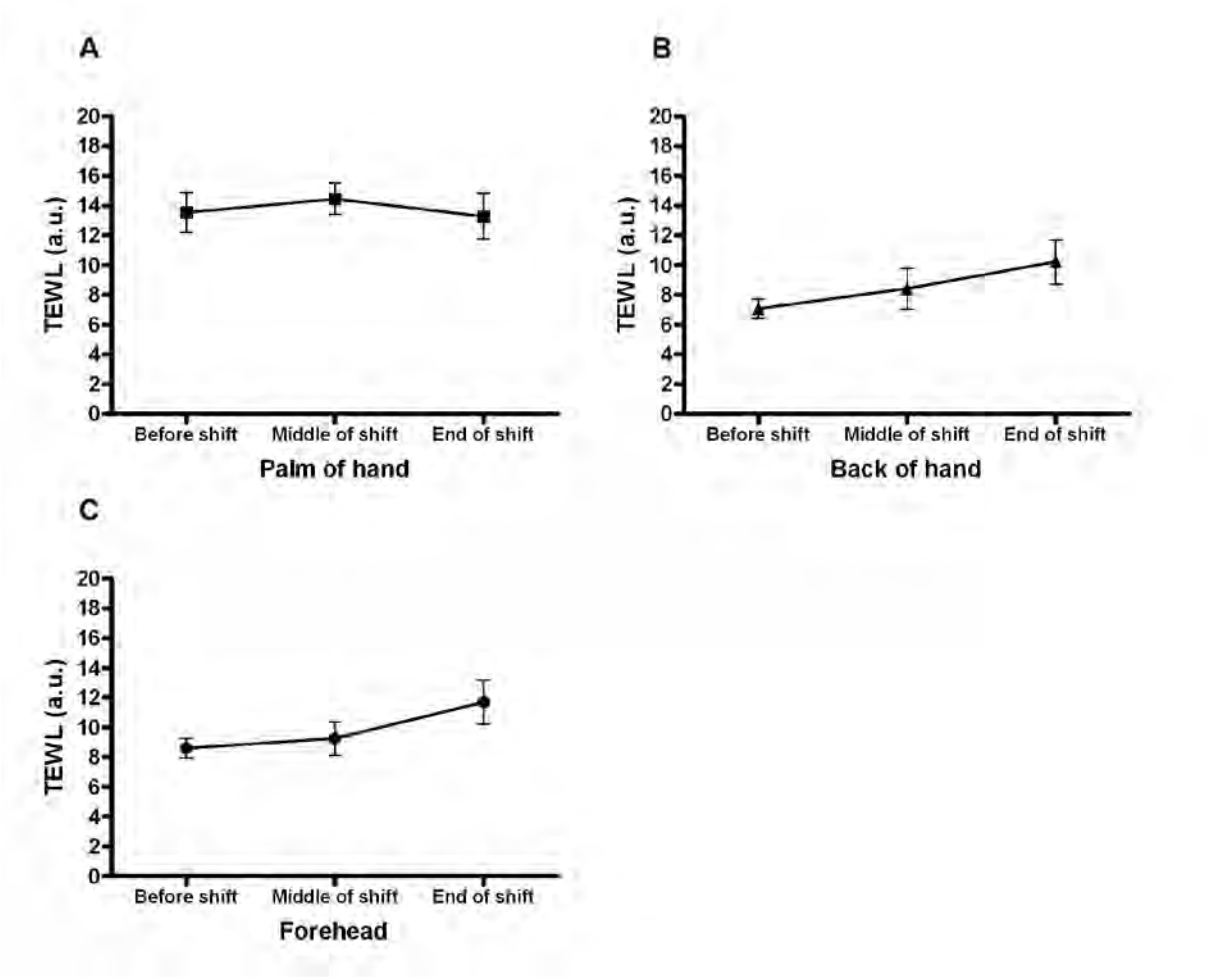

Fig. 2. TEWL index (estimated mean ± SEM) for the (A) palm of the hand, (B) back of hand, and (C) forehead (n =13).

Mean skin surface pH measured before the shift ranged between 5.81 ± 0.03 for the palm of the hand (Fig. 3A) and 5.95 ± 0.07 for the forehead (Fig. 3D). For the palm of the hand, back of the hand and wrist, the skin surface pH decreased throughout the shift. The initial decrease from the start of the shift to the middle of the shift was not statistically significant, but the decrease between the start of the shift and the end of the shift (all p values < 0.01) were highly significant. With the exception of the wrist ($p = 0.08$), the decrease in skin surface pH between the middle of the shift and the end of the shift were also highly significant (all p values < 0.015). The mean forehead pH remained unchanged between the start (5.95 ± 0.07) and middle of the shift (5.95 ± 0.05), but decreased significantly to 5.65 ± 0.05 at the end of the shift.

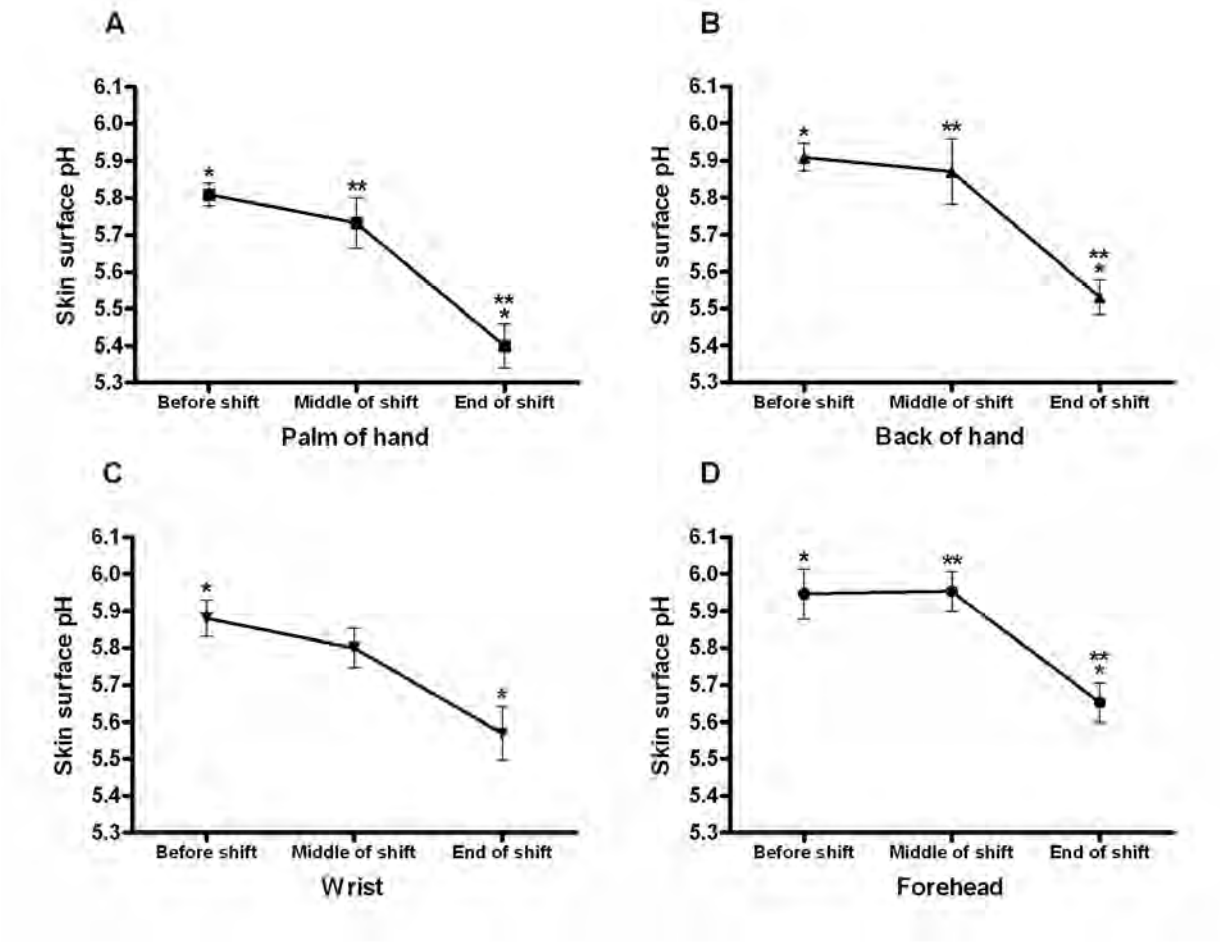

Fig. 3. Skin surface pH (estimated mean ± SEM) for the (A) palm of the hand, (B) back of hand, wrist (C), and (D) forehead (n =13). * and ** indicate statistical significant differences between the means ($P \leq 0.05$).

Correlation of skin condition measurements

Correlations between the palm of the hand, back of the hand, wrist and forehead hydration indices were established by making use of canonical correlations (Table 3). Very high correlations existed between all sets of variables compared, with all canonical R-values between 0.84 (palm of the hand vs. wrist and back of hand vs. wrist) and 1.00 (palm of hand vs. back of hand). The redundancy explains how much of the actual variability in one set of variables (left) are explained by the other set of variables (right). To elaborate, for the wrist, the redundancy shows that an average of 42.3% of the variance in the individual variables of the one group of variables (palm of the hand, left) is explained by the other group of variables (wrist, right). From the other side, 40.0% of the variance in the individual variables of the one group of variables (wrist, right) is explained by the other group of variables (palm of hand, left).

Table 3. Canonical correlations between log-transformed skin hydration measurements.

		Back of hand	Wrist	Forehead
Palm of hand	**Canonical R**	1.00	0.84	0.90
	Redundancy (%)	100.0% / 100.0%	42.3% / 40.0%	52.5% / 52.7%
Back of hand	**Canonical R**		0.84	0.90
	Redundancy (%)		42.3% / 40.0%	52.5% / 52.7%
Wrist	**Canonical R**			0.99
	Redundancy (%)			95.9% / 95.8%

Canonical correlations for TEWL indices is shown in Table 4 and ranged between 0.84 and 0.95, with redundancy of between 32.8% and 58.0%.

Table 4. Canonical correlations between log-transformed TEWL measurements.

		Back of hand	Forehead
Palm of hand	**Canonical R**	0.84	0.84
	Redundancy (%)	35.0% / 32.8%	59.67% / 55.5%
Back of hand	**Canonical R**		0.95
	Redundancy (%)		58.0% / 57.3%

All canonical correlations for skin surface pH measurements were above 0.81 (Table 5). Redundancy was between 22.8% and 56.1%.

Table 5. Canonical correlations between log-transformed skin surface pH measurements.

		Back of hand	Wrist	Forehead
Palm of hand	**Canonical R**	0.94	0.90	0.81
	Redundancy (%)	39.1% / 29.9%	40.5% / 56.1%	22.8% / 27.9%
Back of hand	**Canonical R**		0.99	0.90
	Redundancy (%)		41.5% / 52.7 %	39.5% / 50.8%
Wrist	**Canonical R**			0.84
	Redundancy (%)			41.1% / 41.3%

Skin questionnaire

Six workers responded positively (yes, a little) to only four of the ten questions, namely those referring to troublesome sweating (n = 4), itchy skin (n = 2), dry/sore rash (n = 2) and pimples (n = 2). Four workers indicated that they have experienced these symptoms for more than six months, while the other two workers each indicated that they have experienced it for less than a month or between one and six months respectively. The mean Dalgard score for all the workers is 1.08 ± 0.09 (range 1.0 to 1.2).

Dermal exposure

Dermal exposure to cobalt and nickel is summarised in Table 6 and Table 7. Results of all field blanks analysed were BDL for cobalt and nickel. Forty percent of all dermal wipes analysed for cobalt were BDL and represented samples collected from all anatomical areas and intervals. Only four percent of

samples analysed for nickel were BDL. For cobalt, the highest levels were predominantly collected from the two workers of the cobalt-reduction area, while for nickel, it was all collected from cobalt plant process operators. Cobalt and nickel were collected from all anatomical areas before the shift, with the highest levels removed from the palm of the hand. For cobalt, 11.7 µg cm^{-2} was removed from the palm of one cobalt-reduction area worker prior to the start of the shift. At the same time between 1.92 and 5.56 µg cm^{-2} nickel was removed from the palms of five cobalt plant workers. A very high level of cobalt was removed from the wrist of one worker before the start of the shift. Nickel exceeding 2 µg cm^{-2} was removed from the back of the hands (n = 1), wrists (n = 2) and foreheads (n = 1) of three workers.

More cobalt and nickel, although statistically insignificant, was removed from the palms than the back of the hands in the middle of the shift and at the end of the shift. The levels of cobalt and nickel removed from the wrists and foreheads at the end of the shift were not significantly different from that collected before the shift, although nickel removed from the forehead tended toward significance (*P* = 0.08).

Table 6. Summary of dermal cobalt exposures by anatomical area sampled and sampling intervals.

		µg Co cm^{-2}				
		Median	**Estimated mean**	**SEM**	**Minimum**	**Maximum**
Palm of hand	**Before shift**	0.38	0.34	1.54	BDL (3)	11.71
	Middle of shift	0.77	0.49	1.46	BDL (1)	5.36
	End of shift	0.28	0.32	1.57	BDL (3)	4.20
Back of hand	**Before shift**	0.04*	0.08	1.25	BDL (8)	0.48
	Middle of shift	0.16	0.12	1.27	BDL (4)	0.58
	End of shift	0.04*	0.09	1.42	BDL (8)	1.98
Wrist	**Before shift**	0.04*	0.13	1.59	BDL (8)	8.58
	End of shift	0.12	0.12	1.35	BDL (5)	0.71
Forehead	**Before shift**	0.04*	0.10[a]	1.43	BDL (7)	1.06
	End of shift	0.14	0.17[a]	1.39	BDL (3)	1.48

* Median value represents BDL/2. Numbers in brackets represent the number of samples BDL. a indicates statistical significance (*P* = 0.02)

Table 7. Summary of dermal nickel exposures by anatomical area sampled and sampling intervals.

		µg Ni cm^{-2}				
		Median	**Estimated mean**	**SEM**	**Minimum**	**Maximum**
Palm of hand	**Before shift**	0.73	1.17	1.27	0.27	5.56
	Middle of shift	0.44	0.80	1.44	0.19	8.50
	End of shift	0.63	0.61	1.32	0.16	3.14
Back of hand	**Before shift**	0.35	0.43[a]	1.34	0.13	5.50
	Middle of shift	0.24	0.18	1.55	BDL (1)	0.79
	End of shift	0.12	0.13[a]	1.50	BDL (1)	1.19
Wrist	**Before shift**	0.20	0.15	1.86	BDL (2)	3.16
	End of shift	0.18	0.20	1.64	BDL (1)	2.55
Forehead	**Before shift**	0.37	0.34	1.48	0.02	4.11
	End of shift	0.53	0.51	1.19	0.13	1.90

Numbers in brackets represent the number of samples BDL. a indicates statistical significance (*P* = 0.05)

Correlations between cobalt and nickel exposure for all individual anatomical areas and sampling intervals were established, with only one correlation (palm, end of the shift, r = 0.59) being statistically significant at $P \leq 0.05$ and another (palm, middle of shift, r = 0.54) being significant at $P \leq 0.1$. A highly significant positive correlation [Pearson r = 0.35, $r^2 = 0.12$, P (two tailed) ≤ 0.0001] was established between all cobalt and nickel dermal exposure measurements, irrespective of anatomical area and sampling interval.

Surface exposure

Cobalt and nickel were detected on surfaces that workers are likely to come in contact with on a daily basis. On surfaces such as door handles and staircase hand-rails the amount of cobalt collected on surface wipes ranged between 715.4 µg and 2095.1 µg, while for nickel it ranged between 688.8 µg and 2538.9 µg. The amounts of cobalt and nickel collected from the table surface in the control room of the cobalt plant were 0.107 µg Co cm^{-2} and 0.104 µg Ni cm^{-2}, while 276.9 µg Co and 1458.5 µg Ni were collected from the one computer keyboard. Table surface contamination in the control room of the cobalt-reduction area was much higher, with 0.285 µg Co cm^{-2} and 0.205 µg Ni cm^{-2} collected. Surface samples from the table surface and keypad of the microwave in the kitchen area next to the cobalt plant control room were all BDL for cobalt and nickel.

Cobalt was collected from the digital scale display (65.9 µg), computer keyboard (48.2 µg) and the area around the keyboard (4.5 µg) in the weighing area in the cobalt-reduction area. However, all results were below the BDL for nickel. Samples were also taken from the side (n = 3) and top surfaces (n =3) of empty and filled cobalt packaging drums (250 kg). With the exception of one sample from the side of a filled drum (5.535 µg Co cm^{-2}), all other samples were BDL for cobalt and nickel.

DISCUSSION

Statistical analysis of skin hydration, TEWL and skin surface pH were conducted on the measurements of all participating workers as a group because of the small numbers for some of the job categories and because there were no apparent differences between the skin condition measurements of the workers of the cobalt plant and reduction area or the female and Caucasian worker. Furthermore, the laboratory in which the laboratory analyst performed analysis is located in the cobalt plant (adjacent to the control room) and the laboratory analyst frequently entered the process area to collect samples for analysis.

Skin hydration, TEWL and skin surface pH may be influenced by numerous individual and environmental factors. The most important individual factors are age (Farinelli and Berardesca, 2006; Fluhr *et al.*, 2006), gender (Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006; Fluhr *et al.*, 2008), ethnicity (Berardesca and Maibach, 2003; Schmid-Wendtner and Korting, 2006; Fluhr *et al.*,

2008) and anatomical area (Agache, 2004; Barel and Clarys, 2006; Farinelli and Berardesca, 2006; Schmid-Wendtner and Korting, 2006). For some of these factors, however, published data are conflicting and the reasons for it are beyond the scope of this paper. Environmental temperature and relative humidity, and their seasonal variation, are the most prominent environmental factors that may influence skin hydration and TEWL (Gabard and Treffel, 2004; Barel and Clarys, 2006; Tupker and Pinnagoda, 2006). Where applicable the influence of the above mentioned factors were considered and discussed. However, we consider explaining changes in skin condition during the shift to be more meaningful as this is indicative of changes due to potential exposures in and around the workplace.

Normal skin hydration is necessary for corneocyte differentiation and desquamation (Verdier-Sévrain and Bonté, 2007) as well as maintenance of the skin barrier (Fluhr *et al.*, 2008). Thus, slightly dry or dry skin, as measured before and during the shift on some anatomical areas, may affect skin barrier function negatively. The lower hydration levels (slightly dry to very dry skin) measured on the hands and wrist before the shift may be explained by seasonal variations associated with skin hydration measurements, with higher levels associated with the summer (Barel and Clarys, 2006). Results from this study could also be linked to the explanation given by Du Plessis *et al.* (2010), who pointed out that from a pure economic perspective (i.e. monthly income) skin care may not be a high priority for (African) refinery workers. Only the hydration index of the back of the hand deteriorated significantly during the shift, which corresponds with the general trend reported by Du Plessis *et al.* (2010) for a group of workers at another base metal refinery. However, in this study, hydration of the palm of the hand and wrist did not deteriorate during the shift. Furthermore, in this study, there was no recovery or increase in hydration indices toward the end of the shift as described by Du Plessis *et al.* (2010), which in this study is most likely attributable to a constant workload for the duration of the shift. Hydration indices of this study indicate a perfect correlation between the palm and back of the hand, while correlations between other anatomical areas were also very good.

Recently, Du Plessis *et al.* (2010) reported highly significant increases in TEWL and thus deterioration of skin barrier function for the index finger, palm of the hand and forehead of refinery workers. In this study low skin barrier function, indicative of strained skin condition, was measured for the palm of the hand throughout the shift. Back of the hand and forehead TEWL indices increased, although statistically insignificant, from the beginning to the end of the shift, reflecting deterioration from healthy skin condition with good barrier function to normal skin condition and barrier function at the end of the shift. If the shift duration is prolonged, such as through working “over-time”, and the trend of TEWL for the back of hand and forehead persists, the skin barrier will in all likelihood become compromised and in all likelihood become more permeable to substances. Good correlations existed between palm, back of the hand and forehead TEWL measurements.

Skin surface pH is considered to be an important regulator of the formation of the skin barrier and control of resident microbes, but also prevents colonisation by pathogenic microbes (Agache, 2004; Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006). An optimal pH is required to activate lipid enzymes responsible for processing secreted lamellar bodies and, therefore, the formation of the skin barrier (Fluhr *et al.*, 2006; Feingold, 2007). Normal skin surface pH ranges between 4.2 and 6.1 (median = 5.3), depending on the anatomical area (Agache, 2004b, Schmid-Wendtner and Korting, 2006). With the exception of measurements on the foreheads of four workers, all skin surface pH levels measured before and during the shift fell within the range of normality in spite of a significant decrease in the skin surface pH toward the end of the shift. Possible circadian rhythms for skin surface pH have been reported, with a 0.4 pH unit variation within a 24 hour period. However, the time of day for maximum and minimum levels differ from study to study (Fluhr *et al.*, 2006). Skin surface pH was measured during different shifts which should, therefore, nullify such variation in skin surface pH due to a circadian rhythm. It is more likely that skin exposure to an acidic process solution, most notably sulphuric acid, or its vapours are responsible for this significant decrease in skin surface pH during the shift.

The mean Dalgard score for all participating workers as well as their individual scores were below the threshold of 1.3, which indicates that these workers are of the opinion that their skin condition is healthy and that they are not at risk of developing skin diseases.

Cobalt dermal exposure is characterised by 40% of all samples collected being BDL, while only 4% of nickel samples were BDL. This could be attributed to the ICP-AES being less sensitive for cobalt than nickel. Results indicate that these refinery workers are exposed to cobalt and nickel despite of wearing protective gloves. Of particular concern is the presence of high levels of cobalt and nickel on the skin of workers before the shift. High levels of surface contamination have been measured on hand-rails of stairs, door handles and computer keyboards which could logically explain the high levels of both metals on hands and wrists. For safety reasons workers are encouraged by the employer to use hand-rails of staircases. Another explanation might be handling of contaminated protective clothing or equipment prior to providing samples. The high levels of contamination on the forehead may possibly be due to contamination of hard hats.

Dermal exposure to cobalt and nickel showed high variation in dermal exposure between workers which corresponds with the results of other studies (Day *et al.*, 2009; Du Plessis *et al.*, 2010; Hughson *et al.*, 2010; Julander *et al.*, 2010). More importantly though is that these refinery workers are co-exposed to these two sensitising metals. Results signify that dermal exposure to nickel was consistently higher than that of cobalt for all anatomical areas and intervals sampled and a highly significant correlation (Pearson r = 0.35, P = 0.0001) existed between the two metals' exposure. In

addition, high levels of nickel exposure occurred in areas where nickel contamination was not expected. Concurrent allergy to cobalt and nickel, due to co-sensitisation, has been reported (Lidén and Wahlberg, 1994; Walhberg and Lidén, 2000) and it may enhance the severity of the ensuing dermatitis (Ruff and Belsito, 2006).

To date, efforts to establish a scientific threshold for skin sensitisation and elicitation caused by direct and prolonged skin contact with nickel has been unsuccessful, but for risk characterisation purposes in occupational scenario's a no observed effect level of 0.3 µg Ni cm^{-2} is suggested (DEPA, 2008). This value was derived from occluded patch testing over 48 hours with nickel sulphate in nickel-sensitive subjects. Results of this study reveal that 65.9% (81 of 123) of samples collected from cobalt plant workers were above the threshold. For cobalt a similar no observed effect level is not known, although Allenby and Basketter (1989) and Julander *et al.* (2009) elicited allergic contact dermatitis reactions in cobalt-sensitised persons with cobalt chloride at 0.5 µg cm^{-2}. If this is used as a hypothetical no observed effect level, 22% (27 of 123) of all samples collected in this study exceeded the threshold. Despite the high percentage of nickel samples exceeding the no observed effect level, co-exposure to both metals and skin condition that may lead to increased skin permeation and absorption (compromised skin), the incidence of allergic contact dermatitis is low and in agreement with the low number of allergic contact dermatitis cases reported for metal workers by Shum *et al.* (2003). Hughson *et al.* (2010) questioned the validity of the no observed effects level for nickel in occupational settings, stating that occupational exposure are less concentrated, lack occlusion and duration of contact. Furthermore, the no observed effects limit is derived from elicitation reactions in nickel-sensitised subjects (DEPA, 2008). Hughson *et al.* (2010) argues further that the threshold for inducing nickel sensitisation is expected to be higher than the threshold for elicitation. Thus, the low incidence of allergic contact dermatitis in metal workers is due to the sensitising (induction) threshold for nickel and/or cobalt not being exceeded. In this study this could also be the case, but ethnic differences in skin structure and function have been reported. Stratum corneum function is considered to be stronger in subjects with darker skin upon chemical or mechanical challenge (Rawlings, 2006). Although published results on the incidence of allergic contact dermatitis in blacks are conflicting (Berardesca and Maibach, 2003), Dogliotti (1970) reported lower incidences in black South Africans. Ethnic differences in skin structure and function may decrease the likelihood of African workers developing allergic contact dermatitis.

CONCLUSIONS

All forehead skin hydration indices were normal, while indices for the hands (palm and back of the hand) and wrist, before and during the shift indicated various degrees of skin dryness and possible impaired barrier function. TEWL indices for the palm of the hand represented strained barrier function before and during the shift, but forehead and wrist skin barrier function remained within a

healthy to normal range. Skin surface pH for all anatomical areas sampled decreased significantly during the shift, but remained in normal range. Cobalt and nickel were collected from the skin even before the start of the shift, but highly variable skin loading of the two metals occurred during the shift on all anatomical areas sampled. Furthermore, dermal exposure to nickel was consistently higher than that of cobalt for all anatomical areas and intervals sampled. Slightly damaged, compromised skin may lead to increased skin permeation and absorption of cobalt and nickel present on the skin and thus increase the risk of developing allergic contact dermatitis. The risk is further increased by the co-exposure to nickel and cobalt. Despite the skin condition and high levels of dermal exposure reported, the incidence of allergic contact dermatitis at the base metal refinery is very low. Ethnic differences in skin structure and function may decrease the likelihood of African workers developing allergic contact dermatitis.

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Chapter 7: Article IV

Du Plessis JL, Eloff FC, Laubsher PJ, van Aarde MN, Franken A. (2010) Comparison of South African skin and sensitisation notations with other countries. Occup Health SA; 16(May/June):18-24.

7.1 Background

In South Africa, occupational exposure limits (OELs) and skin and sensitisation notations for the general industry (non-mining) are published in the Regulations for Hazardous Chemical Substances (1995) under the Occupational Health and Safety Act (Act 85 of 1993), while for the mining industry they are published in the Mine Health and Safety Regulations of the Mine Health and Safety Act (Act 29 of 1996). Whilst conducting research on dermal exposure to metals (nickel and cobalt), differences in the assignment of skin and sensitisation notations between these Regulations and other countries became apparent. It raised the question of whether this is also true for other substances and if so, to what extent?

7.2 Instructions to authors

Refer to Chapter 4 for the journal, Occupational Health Southern Africa's instructions to authors.

ORIGINAL RESEARCH

PEER REVIEWED

Comparison of South African skin and sensitisation notations with those of other countries

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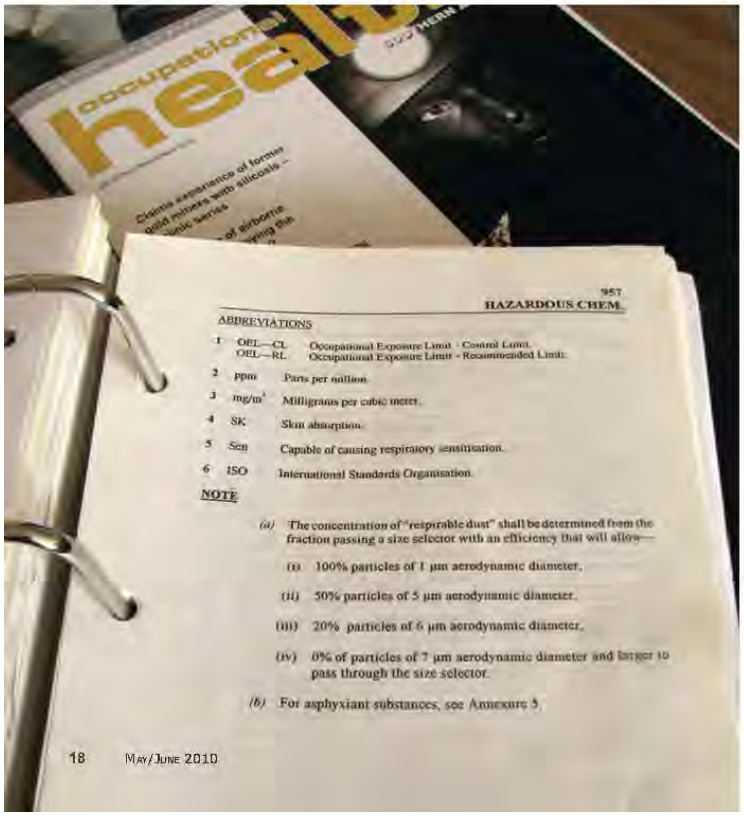
Abstract

South African skin notations listed in the Regulations for Hazardous Chemical Substances (RHCS) and Mine Health and Safety Regulations (MHSR) were compared to those of selected other developed countries in order to ascertain the assignment criteria and use of these notations relative to those of other countries. Skin notations in the RHCS and MHSR had a mean agreement of between 42.9% and 45.8% with other countries, while agreement for sensitisation notations was only 3.6% between countries. As with many other countries there is a lack of frequent review and updates of these notations. Thus, there is an urgent need to develop and implement a strategy which will ensure frequent revision of assignment of notations accompanied by accessible supporting documentation. Adoption of the USA's National Institute for Occupational Safety and Health skin notation criteria is recommended, whereby substances may be assigned with multiple descriptive skin notations. The development of similar sensitisation notation criteria whereby the route of exposure is indicated is also recommended.

Key words: skin notation, sensitisation notation, comparison, countries

Introduction

In South Africa, occupational exposure limits (OELs) and skin and sensitisation notations for the general industry (non-mining) are published in the Regulations for Hazardous Chemical Substances (1995)[1] under the Occupational Health and Safety Act (Act 85 of 1993), while for the mining industry they are published in the Mine Health and Safety Regulations[2] of the Mine Health and Safety Act (Act 29 of 1996). Hereafter, reference will only be made to the abbreviations, RHCS and MHSR for simplicity. Whilst conducting research on dermal exposure to metals, differences in the assignment of skin and sensitisation notations between the RHCS, the MHSR and other countries became apparent. It raised the question of whether this is also true for other substances and if so, to what extent?



The history of skin notations associated with OELs can be traced back to 1958, when the approach was first introduced by Germany. In 1961, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted the same approach.[3] The only original intention of a skin notation was for it to be used as a qualitative warning sign, indicating that a specific substance may penetrate the human skin with the potential of contributing significantly to total systemic toxicity.[3,4]

At present skin notations are associated with almost every country's list of OELs, but assignment thereof by countries is inconsistent.[3,5] Clearly defined, universal (world-wide) criteria for assignment of skin notations do not exist and in some instances, incorrect assignment of notations to substances causing skin irritation, corrosion and sensitisation has also occurred.[3] However, insufficient information on skin absorption rates of substances has also contributed to the inconsistent assignment.[3,6] Numerous scientific papers, scientific committees and commissions have proposed strategies for improved, "harmonised" assignment and use of skin notations.[3,7-12] Universal criteria for assignment of skin notations would ensure consistent assignment and use thereof globally as qualitative warning signs. In particular, improvement in the

assignment and use of skin notations has been recommended by the National Institute for Occupational Safety and Health (NIOSH) skin notation criteria.[13]

In general, a sensitisation notation refers to the potential of a substance to produce sensitisation.[14] Sensitisation occurs through immunologic mechanisms. Initially, upon exposure to a sensitiser, little or no response is observed. However, after sensitisation has occurred, subsequent exposure to the sensitiser, even at minute concentrations (even far below the OEL), may elicit a response also known as a hypersensitivity reaction. These hypersensitivity reactions may have an immediate (e.g. asthma, rhinitis) or delayed onset (e.g. skin rash). Unlike skin notations, there is no published literature comparing sensitisation notations of different countries.

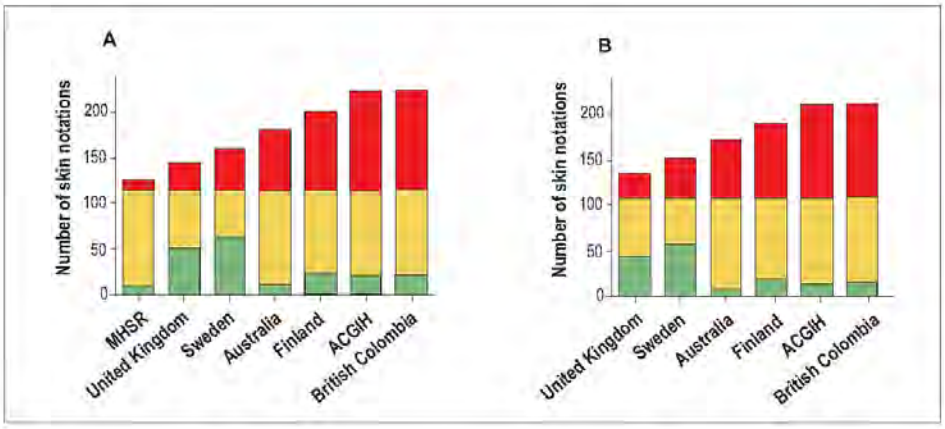
The aims of this study were to quantitatively and qualitatively compare South African skin notations and sensitisation notations with those of other selected developed countries in order to ascertain the assignment criteria and use of these notations relative to those of other developed countries.

Methodology

The most recent published lists of OELs with skin and sensitisation notations from South Africa,[1,2] the United Kingdom,[15] Sweden,[16] Australia,[17] Finland,[18] British Colombia (Canada)[19] and the ACGIH (United States of America)[14] were used. With the exception of Australia, the other countries or institution were selected as representatives of developed countries in North-America and Europe, all with reputable occupational hygiene standards. Comparisons were made between the use of skin notations and sensitisation notations in these countries, based on the names of substances published in the lists. CAS numbers were used to identify chemicals listed under different (synonymous) names. Isomeric compounds were either grouped by some countries or individually listed by others. Where possible, data were adjusted by grouping isomeric substances, thereby giving the combined group of isomers a skin notation or sensitisation notation. Consequently, there may be differences in the numbers stated here for each country from those published in the national lists. These differences are considered to be small and of minor importance when major differences between countries are discussed.[1] In this study the percentage agreement between two countries/institutions was calculated based on the number of substances sharing a notation in relation to the sum of the substances with a shared notation and those only listed by the two countries as depicted by the following formula:

$$\% \text{ Agreement} = \frac{\text{number of substances listed with a shared notation in RHCS and other country}}{\text{number of substances listed only in RHCS + shared + listed only by other country}} \times \frac{100}{1}$$

Thus, the absence from the list of OELs in one country (i.e. no OEL or skin notation) but presence of an OEL with a skin notation in that of the other country is considered a disagreement. The same is true if both countries list an OEL for a substance, but only one assigns a skin notation. Irrespective of whether a country/institution has evaluated a substance or not, the absence of a substance in one country's list of OELs is considered as not recognising any hazard



Key
Green bars – the number of substances with a skin notation listed only in South Africa (RHCS in A and MHSR in B).
Red bars – the number of substances with a skin notation listed only in the other country (or MHSR in A).
Orange bars – the number of substances with a skin notation in both countries, i.e. "overlap"/agreement.

Figure 1. The number of substances with a skin notation in South Africa compared with other countries. (A) RHCS compared to MHSR and other countries. (B) MHSR compared to other countries

or risk associated with inhalation and/or skin exposure as identified by other countries/institutions.

Results

Skin notations

A total number of 115 and 112 substances with skin notations are listed in the RHCS and MHSR respectively. Both lists share 103 substances, with 12 being listed only by the RHCS and nine being only listed by the MHSR (Figure 1A, first bar). The agreement or "overlap" between these two lists is 83.1%. However, when the lists of RHCS (Figure 1A) and MHSR (Figure 1B) are compared to those of other countries, there is far less agreement and it varies between 32.7% and 57.2% for the RHCS (mean of 42.9%) and between 33.3% and 58.2% for the MHSR (mean of 45.8%). In both cases, the smallest agreement is with Sweden and the highest agreement with Australia.

The differences in skin notations between countries are further highlighted when the number of substances with skin notations common to the countries is examined (Figure 2). The total number of substances listed by the RHCS and the six other countries is 292, whilst the total listed by the MHSR and the six other countries is 289. For the comparison of the RHCS with other countries, 50 substances with a skin notation are listed by only one of the seven countries, while 51 substances are listed for the MHSR comparison with other countries. Remarkably, in both comparisons, only 27 substances (9.3%) of all the

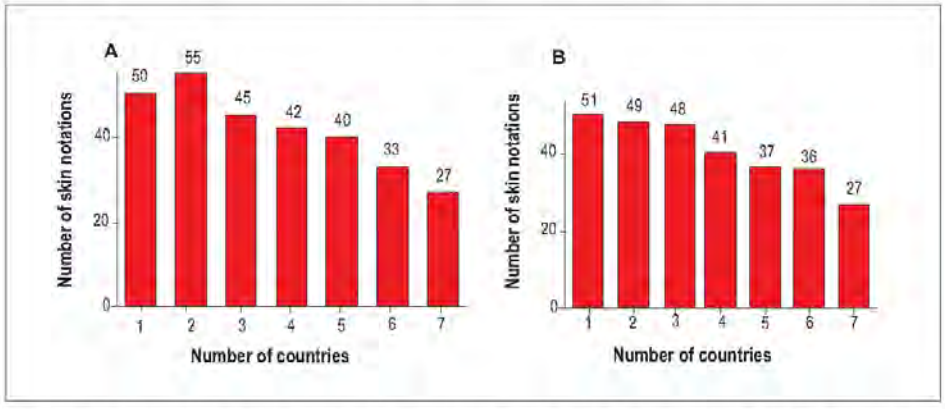
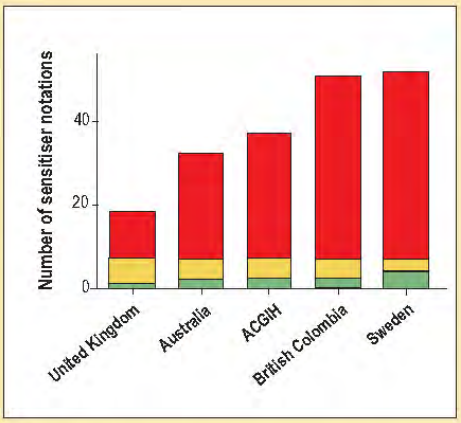


Figure 2. Comparison of the number of substances listed with a skin notation with the number of countries in which they are listed. (A) RHCS and the six other countries (n = 292). (B) MHSR and the six other countries (n = 289)



Key
Green bars – the number of substances with a sensitisation notation listed only in the RHCS and MHSR
Red bars – the number of substances with a sensitisation notation listed only in the other country
Orange bars – the number of substances with a sensitisation notation in both countries, i.e. "overlap"/agreement.

Figure 3. The number of substances with a sensitisation notation in South Africa as compared with other countries

substances with a skin notation appear in all seven of the countries' lists.

Skin notations were also compared with respect to definitions and criteria used to assign them. In the MHSR, a skin notation is only explained by the phrase "danger of cutaneous absorption".[2] The RHCS contains the wording "skin absorption" with further explanation thereof in paragraph 40. This paragraph (adopted from the United Kingdom) states that substances with a skin notation have the ability to penetrate the intact skin upon localised contamination (i.e. splashes on the skin or clothing or in certain cases to high airborne vapour concentrations) and, therefore, become absorbed into the body.[1] However, in the United Kingdom specific reference is also made to skin absorption leading to systemic toxicity. The criteria used for assignment of a skin notation in the United Kingdom are based on available data/experience/predictions which suggest a substantial contribution of the skin exposure route to body burden (compared to the airborne exposure at the OEL) and causing systemic effects. This implies that assessment of airborne exposure concentrations alone may be insufficient in describing exposure and the health effects.[15] In Sweden reference is only made to substances which can easily be absorbed percutaneously.[16] The Finnish notation refers to absorption through the skin causing health effects.[18] Skin notations in Australia, British Colombia (Canada) and the ACGIH refer to substances that contribute significantly to the overall exposure by the cutaneous (skin) route.[14,17,19] British Colombia and the ACGIH explain exposure as being through direct skin contact (solids, liquids) or vapour and includes contact with the mucous membranes of the eyes.[14,19] Additional explanations of direct effects of certain substances (e.g. dermal irritants) on the skin and mucous membranes as well as substances functioning as vehicles or enhancers of penetration (i.e. solvents) are included by Sweden, Australia and the ACGIH.[14,16,17]

Sensitisation notations

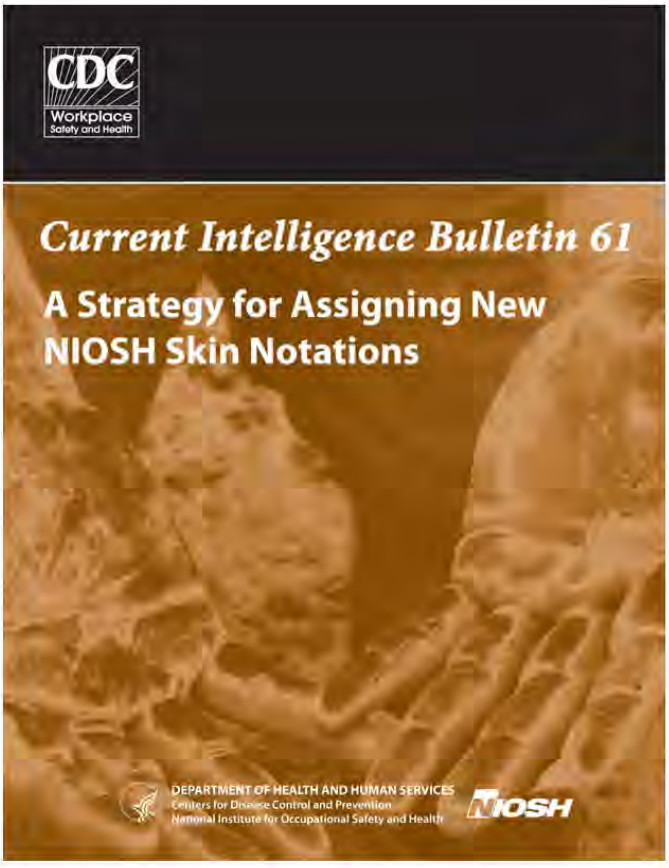
The only difference between the RHCS and MHSR sensitisation lists is that the RHCS lists isocyanates as a group (as –NCO) as well as six individual isocyanate compounds, each with their own sensitisation notation, whereas MHSR have only one notation for isocyanates (as –NCO). Only the RHCS, Sweden and British Colombia listed individual isocyanate compounds with sensitisation notations and it was, therefore, decided to consider isocyanates as a group in this study. It also means that in this study there is no difference between the sensitisation lists of the RHCS and MHSR, with both listing seven substances. A formal sensitisation notation is not listed by Finland, only standard risk phrases relating to the special risks attributed to dangerous substances and preparations. It was, therefore, not included in this data set.

The overlap between the South African lists (RHCS and MHSR) and those of other countries ranges between three and six substances (mean 4.8) with one to four substances only being listed in the South African Regulations (Figure 3). Eleven, 44 and 45 substances listed by the

United Kingdom, British Colombia and Sweden, respectively, do not appear in the RHCS or MHSR.

Figure 4 illustrates that of the 84 substances with a sensitisation notation, 32 (38.1%) are listed by only one country. Surprisingly, only three substances are listed by all six countries, representing 3.6% of all substances listed with a sensitisation notation. These three substances are phthalic anhydride, trimellitic anhydride and the group of isocyanates (-NCO).

According to definitions, the notation of sensitisers by countries can be divided into those only listing respiratory sensitisers causing occupational asthma (i.e. RHCS, United Kingdom) and those listing the substances merely as sensitisers (MHSR, Australia, Sweden, British Colombia and ACGIH). The assigned sensitisation notation in the United Kingdom is accompanied by risk phrases warning against sensitisation through inhalation (R42) and sensitisation through inhalation and skin contact (R42/43). Five substances without a notation, but with a R43 risk phrase (sensitisation through skin contact) are also listed by the United Kingdom.[15] Sensitisation notation by the ACGIH refers to the potential for a substance to produce sensitisation, as confirmed by human or animal data. The notation does not distinguish between the routes of exposure nor to the reactions.[14] British Colombia documentation states that it covers all ACGIH-identified sensitisers, yet when analysed there are significant differences (British Colombia list a total of 49 and ACGIH 35, with 2 only listed by ACGIH and 16 only by British Colombia). In Sweden and Australia, the skin and respiratory organs are named as positions of hypersensitivity reactions.[16,17] Furthermore, apart from providing a list of substances with sensitising properties, Sweden also provides a separate list, containing names of highly sensitising substances, for which permission from authorities must be obtained before being handled.[16]



Discussion

Skin notations

Nielsen and Grandjean compared skin notations of five European countries with that of the ACGIH. They found that agreement ranged between 24.8% (Slovenia) and 61.6% (Denmark) with a mean of 40.4%.[1] Agreement of the RHCS with other countries was slightly higher (42.9%), while that of the MHSR was 45.8%. The low agreement of South African RHCS and MHSR lists with those of Australia, Finland, ACGIH and British Colombia (Canada) is attributed to the number of substances only appearing in the lists of the other countries, ranging between 65 to 109 for RHCS and 65 to 106 for MHSR. One of the main reasons given by Nielsen and Grandjean for the lack of agreement relates to differences in the written criteria used for assigning skin notations.[3] From our results it is clear that there are sometimes subtle differences in the interpretation and intention of the criteria used to assign skin notations between countries. According to definitions and explanatory documentation of countries showing large disagreements with South African notations, it is not that skin notations are incorrectly assigned to for instance skin irritants and corrosive substances. However, the ACGIH assigns skin notations to substances with an acute dermal lethal dose (LD_{50}) < 1000 mg/kg. Furthermore, British Colombia and the ACGIH clearly include contact with mucous membranes of the eyes as skin contact. The lack of proper data on skin permeability/penetration for many substances has also been implicated as a reason for lack of agreement.[3,6] In addition, reasons for assignment or non-assignment are not always accompanied by specific reference to documentation and arguments.[3] This lack of transparency makes it impossible to trace why substances were or were not given a notation but also to establish when last assignments were made. Yearly additions and retractions are only evident for the ACGIH. Unfortunately, neither the

RHCS nor the MHSR provide supporting documents explaining assignment or non-assignment for individual substances. Not only in South Africa, but also in other countries, there is thus an urgent need to develop and implement a strategy which will ensure frequent revision of assignment of skin notations accompanied by accessible supporting documentation.

NIOSH published a new strategy for assigning skin notations in 2009.[13] Based on scientific evidence the existing 142 substances currently listed by NIOSH and other substances will be assigned with multiple (or combined) skin notations distinguishing between effects caused by exposure (Table 1). Substances for which insufficient data associated with skin exposure exist will also be identified. A notation (SK) for a substance not posing a skin health risk (based on current knowledge) will also be assigned.

The skin is also often exposed to mixtures of substances and assessing it will prove as complex as dealing with airborne exposures to mixtures of gases or vapours.[3,11] The NIOSH skin notation criteria do not incorporate a notation for substances known to enhance the skin permeation of other substances. However, such a notation may easily be incorporated in future.

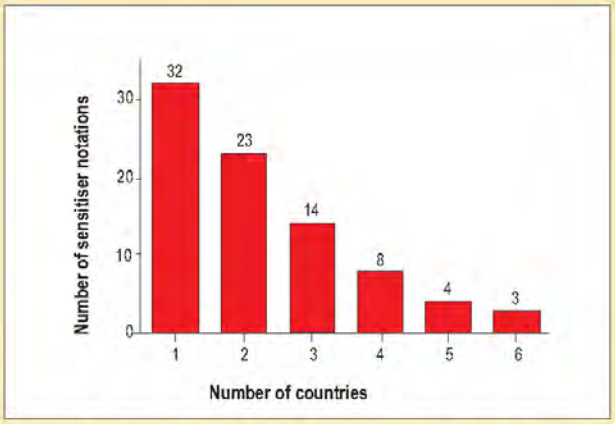


Figure 4. Comparison of the number of substances with a sensitisation notation (n = 84) with the number of countries in which they are listed

". . . only three substances are listed with a sensitisation notation by all six countries."

Sensitisation notations

As already noted, there is no published literature comparing sensitisation notations of different countries. The lack of disagreement for sensitisation notations between countries is quite astounding. This is further accentuated when sensitisers listed by other countries in this study (excluding RHCS and MHSR) are compared. The list of sensitisers listed by all five countries only increased to five substances (6% of all substances listed), adding gluteraldehyde and maleic acid to the existing three substances. If the United Kingdom is also excluded, the list increased to ten substances (12.3% of all substances) for the four countries (adding formaldehyde, methyl acrylate, n-butyl glycidyl ether, phenyl glycidyl ether and turpenes). The lack of human evidence is even more pronounced in skin sensitisation and allergic contact dermatitis[11] which may explain the necessity to rely heavily on predictions and animal data, which in turn lead to varied often subjective interpretation and assignment of notations. The lack of accompanying documentation and, therefore, transparency may also contribute toward this situation.

Alarmingly, the RHCS only acknowledges sensitisation through inhalation. Although not implied by the

Table 1. Skin notations assignment according to NIOSH.[13]

Abbreviation	Explanation
ID(SK)	After evaluation, insufficient data exist to assess the skin exposure hazard accurately.
ND	Not evaluated by this strategy and the health hazard associated with skin exposure is unknown.
SK	Skin notation.
SK	Indicating that reviewed data did not identify a health risk associated with skin exposure.
SK:DIR	Potential for direct effects to the skin following contact with a substance.
SK:DIR (COR)	Potential for a substance to be corrosive following skin exposure.
SK:DIR (IRR)	Potential for a substance to be a skin irritant following skin exposure.
SK:SEN	Potential for immune-mediated reactions following exposure.
SK:SYS	Potential for systemic toxicity following skin exposure.
SK:SYS (FATAL)	Highly or extremely toxic substance and may be potentially lethal or life threatening following skin exposure.

definition, the same is also true for the MHSR because of the identical lists of sensitisers.

Conclusions and recommendations

Skin notations in the RHCS and MHSR only had a mean agreement of between 42.9% and 45.8% with those of other countries, while only 3.6% agreement existed for sensitisation notations. It is also clear that there are sometimes subtle differences in the interpretation and intention of the criteria used to assign skin notations between countries. As with many other countries there is a lack of frequent review and updates of these notations, therefore, there is an urgent need to develop and implement a strategy which will ensure frequent revision of assignment of skin notations accompanied by accessible supporting documentation. Adoption of the NIOSH skin criteria for use in South Africa is recommended. It is recommended that all sensitisers, irrespective of the route of exposure, should be acknowledged and incorporated in the RHCS and MHSR and other legislation. The development of multiple sensitisation notation criteria whereby the route of exposure, i.e. respiratory (SEN:RES) and skin (SEN:SK) or a combination thereof (SEN:RES/SK) for inclusion in the RHCS and MHSR is also recommended. This will enable occupational hygienists to distinguish more efficiently between different skin and sensitisation hazards, thereby enabling them to assess and control exposure more appropriately.

Lessons learned

1. **Clearly defined, universal criteria for assignment of skin notations do not exist.**
2. **The absence of a skin notation for a substance does not necessarily imply the absence of a skin hazard.**
3. **Sensitiser notations in the RHCS and MHSR only refer to respiratory sensitisers and not to skin sensitisers.**
4. **The assignment and use of a skin or sensitiser notation in one set of regulations or country is not necessarily the same as for another set of regulations or country.**

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Chapter 8: Conclusions, recommendations, limitations and future studies

In this final chapter, conclusions will be made with specific reference to the aims, objectives and hypotheses postulated for this thesis. Recommendations, in particular those made to the base metal refineries (employer) in an attempt to reduce dermal exposure to nickel/cobalt and to improve skin condition of exposed refinery workers (employees), are given. Finally, limitations of this thesis/study and possible future studies will be discussed.

8.1 Conclusions

A review of literature pertaining to the different methods used to assess dermal exposure to substances is given in the Chapter of the MHSC Handbook on Mine Occupational Hygiene Measurements (Chapter 3 of this thesis) and the review article (Article I, Chapter 4 of this thesis) published in the journal *Occupational Health Southern Africa*. Furthermore, methods used specifically to assess dermal exposure to cobalt and nickel are given in Section 2.3.1 of Chapter 2. To conclude, dermal exposure has been reported for numerous occupational and environmental substances by making use of surrogate skin methods (interception methods), removal methods and fluorescent tracer methods (*in situ* detection methods) (Fenske, 1993; Brouwer *et al.*, 2000; Cherrie *et al.*, 2000; Soutar, 2000; ECS, 2006). From published literature it is evident that skin (dermal) wipes, as a removal method, are the most appropriate method to assess dermal exposure to metals. At present one of the major issues regarding assessment of dermal exposure is the lack of universally recognised and accepted standardised methods. For skin (dermal) wipes, as a removal method of metals, major differences between studies have been reported and include the validation of the method (refer also to the discussion of Article II), the type of wipe used, the number of wipes per sample, the number of times an area must be wiped consecutively, the anatomical areas sampled, the surface area of samples and the measurement unit of results.

Only a few publications have reported the occupational dermal exposure to nickel and/or cobalt. These publications assessed dermal exposure of carpenters, cashiers, locksmiths and workers involved in the production of cemented-carbides, gas turbines and space propulsion components (Lidén *et al.*, 2008; Day *et al.*, 2009; Julander *et al.*, 2010). The only other study assessing dermal exposure of European refinery workers to nickel was recently published in the *Annals of Occupational Hygiene* (Hughson *et al.*, 2010). One set of dermal exposure results, presented in Chapter 5 (Article II) of this thesis, was published in the same issue of the above mentioned journal. Results indicated that a group of refinery workers, i.e. cell-workers, involved in the electro-winning of nickel are exposed to nickel

through the skin exposure route. Nickel was removed from the index fingers, palm of the hand, neck and forehead before the start of the shift. Exposure during the shift was highly variable between workers and ranged between 0.236 and 177.77 µg Ni cm^{-2} on the index finger and between 0.045 and 229.86 µg Ni cm^{-2} on the palm of the hand. Nickel removed from the neck and forehead at the end of the shift was significantly higher than that removed before the shift.

The second set of dermal exposure results, presented in Chapter 6 (Article III) will be submitted for publication in the near future. The sampling strategy differed from Article II with regard to the sampling intervals, anatomical areas sampled and the number of consecutive wipes per sample (refer to Section 6.1 for more detail). Results of this study indicated that refinery workers at a cobalt plant are co-exposed to highly variable cobalt and nickel levels through the skin exposure route. Co-sensitisation and concurrent allergy to both metals may occur (Lidén and Wahlberg, 1994; Walhberg and Lidén, 2000). Cobalt and nickel were collected from all anatomical areas before the shift. Exposure ranged between BDL (0.087 µg Co cm^{-2}) and 11.76 µg Co cm^{-2} and 0.16 and 8.50 µg Ni cm^{-2} on the palm of the hand. Lower levels of cobalt and nickel were removed from the back of the hand, wrist and forehead. Furthermore, dermal exposure to nickel was consistently higher than that of cobalt for all anatomical areas and intervals sampled. Consequently, the *first hypothesis*, refinery workers are exposed to sensitising metals (nickel and/or cobalt) through the skin exposure route, is accepted.

Skin hydration and transepidermal water loss (TEWL) are commonly used to assess skin condition and TEWL has been used extensively to evaluate skin barrier function (Zhai and Maibach, 2002; Pirot and Falson, 2004; Levin and Maibach, 2005; Rawlings *et al.*, 2008). The skin surface pH and maintenance thereof is considered to be an important regulator of the formation of the skin barrier (Agache, 2004; Fluhr *et al.*, 2006; Schmid-Wendtner and Korting, 2006; Feingold, 2007). In Articles II and III, skin condition of refinery workers was assessed concurrently with dermal exposure to nickel and/or cobalt. In Article II, hydration indices of the hands decreased significantly from normal and slightly dry to between dry and very dry during the shift, but by the end of the shift it recovered to levels similar to those measured before the shift. Forehead and neck hydration indices were considered to be within normal range throughout the shift. TEWL indices of the index finger and palm of the hand indicated low barrier function even before the shift, which further deteriorated to very low barrier function by the end of the shift. Forehead TEWL indices deteriorated from normal to low barrier function by the end of the shift. The condition of the skin was attributed to inadequate protection provided by gloves and exposure to an acidic (irritant) electrolyte solution. In Article III, all forehead skin hydration indices were normal, while indices for the hands (palm and back of the hand) and wrist, before and during the shift indicated various degrees of skin dryness and possible impaired barrier function. TEWL indices for the palm of the hand represented strained barrier

function before and during the shift, but forehead and wrist skin barrier function remained within a healthy to normal range. Skin surface pH for all anatomical areas sampled decreased significantly during the shift, but remained in normal range. Thus, the *second hypothesis*, the skin condition of refinery workers is indicative of unhealthy skin hydration and skin barrier function which may increase the risk of dermal absorption of nickel and/or cobalt measured on the skin, is partially accepted because in both sets of results one or more skin hydration (forehead, Article II and III) and TEWL (forehead and back of the hand, Article III) indices were normal and remained between normal ranges during the shift. Based on TEWL results, the skin barrier function of electro-winning workers of Article II is lower than that of cobalt plant workers of Article III.

Although permeability of nickel and cobalt through intact skin is considered to be very low, *in vitro* experiments indicate that skin permeation increases significantly through damaged skin (Larese Filon *et al.*, 2009). Therefore, results of skin condition measurements, in particular those of the hands as the body area most likely to come into contact with cobalt and/or nickel, suggest some degree of skin damage and thus increased skin permeation and absorption of cobalt and/or nickel.

For sensitisation to occur, sensitiser metals deposited on the skin must permeate through the stratum corneum and initiate an immune response in the underlying viable tissue. Efforts to establish a scientific nickel salt threshold for skin sensitisation and elicitation caused by direct and prolonged skin contact has been unsuccessful, but for risk characterisation purposes in occupational scenario's a no observed effect level of 0.3 µg cm^{-2} is suggested (DEPA, 2008). This value was derived from occluded patch testing over 48 hours with nickel sulphate in nickel-sensitive subjects. Dermal wipe results from Article II reveal that 82.4% (257 of 312) of nickel samples collected from cell-workers were above this threshold, while 65.9% (81 of 123) of samples collected from cobalt plant workers (Article III) were above the threshold. For cobalt a similar no observed effect level is not known, although Allenby and Basketter (1989) and Julander *et al.* (2009) elicited allergic contact dermatitis reactions in cobalt-sensitised persons with cobalt chloride at 0.5 µg cm^{-2}. If this is used as a hypothetical no observed effect level, 22% (27 of 123) of all samples collected from cobalt and cobalt-reduction plant workers exceeded the threshold.

Despite the high percentage of nickel samples exceeding the no observed effect level (Articles II and III), co-exposure to both metals (Article III) and skin condition that may lead to increased skin permeation and absorption (Articles II and III), the incidence of allergic contact dermatitis is low and in agreement with the low number of allergic contact dermatitis cases reported for metal workers by Shum *et al.* (2003). In light of this, Hughson *et al.* (2010) questioned the validity of the no observed effects level for nickel in occupational settings, stating that occupational exposure are less concentrated, lack occlusion and duration of contact. Furthermore, the no observed effects limit is

derived from elicitation reactions in nickel-sensitised subjects (DEPA, 2008). Hughson *et al.* (2010) argues further that the threshold for inducing nickel sensitisation is expected to be higher than the threshold for elicitation. Thus, the low incidence of allergic contact dermatitis in metal workers is due to the sensitising (induction) threshold for nickel not being exceeded. In this study this could also be the case, but ethnical differences in skin structure and function have been reported. Stratum corneum function is considered to be stronger in subjects with darker skin upon chemical or mechanical challenge (Rawlings, 2006). Although published results on the incidence of allergic contact dermatitis in blacks are conflicting (Berardesca and Maibach, 2003), Dogliotti (1970) reported lower incidences in black South Africans. Ethnical differences in skin structure and function may decrease the likelihood of African workers developing allergic contact dermatitis.

The comparison of South African skin and sensitisation notations with those of selected other developed countries in order to ascertain the assignment criteria and use of these notations relative to those of other countries is presented in Article IV (Chapter 7). Skin notations in the Regulations for Hazardous Chemical Substances (RHCS) and Mine Health and Safety Regulations (MHSR) had a mean agreement of between 42.9 and 45.8% with other countries, while agreement for sensitisation notations was only 3.6% between countries. It is also clear that there are sometimes subtle differences in the interpretation and intention of the criteria used to assign skin notations between countries. As with many other countries there is a lack of frequent review and updates of these notations in South African legislation.

The disagreement in the notations is evident for nickel and cobalt. Of the seven countries included into this study, only the United Kingdom listed nickel with a skin notation, thereby recognising skin absorption. Cobalt is not listed as such by any of the selected countries, even though dermal absorption of cobalt *in vivo* has been reported (Scansetti *et al.*, 1994; Linnainmaa and Kiilunen, 1997).

Cobalt sulphate and cobalt dichloride are listed seperately as a sensitiser by Sweden, while cobalt (and its inorganic compounds) is listed as sensitisers by Australia (metal dust and fume), Sweden (total dust) and the United Kingdom. Although nickel is considered to be the most common contact allergen in the general population and in occupational settings (Thyssen and Menné, 2010), nickel and its soluble compounds (with the exception of nickel carbonyl and –disulphide) are listed as sensitisers by only Australia and Sweden. Occupational exposure to base metals, such as cobalt and nickel, is associated with platinum mining. With South Africa being the world's largest platinum producer the lack of notations, in particular sensitiser notations, for cobalt and nickel in the RHCS and MHSR are of great concern. Alarmingly, the RHCS only acknowledges sensitisation through inhalation. Although not implied by the definition, the same is also true for the MHSR because of the identical lists of sensitisers.

8.2 Recommendations

Recommendations related to the results of Articles II, III and IV will be given in the following text. Recommendations made to the two base metal refineries in an effort to reduce dermal exposure to nickel and/or cobalt and to improve skin condition of exposed refinery workers, will be given separately. The order in which the recommendations are given has no meaning.

8.2.1 Electro-winning plant (tank house): Article II

Recommendation 1: Hand wash facilities in the electro-winning plant (tank house) are inadequate. Next to the entrance to the tea room there is only one basin and tap which all workers must use to wash their hands before entering the tea room area. It is recommended that more basins be installed.

Recommendation 2: Manual opening and closing of the tap is a potential source of hand contamination. The tap is opened with contaminated/dirty hands, washed and then needs to be closed again. It is recommended that a foot-operated pedal system be installed to open/close the tap. This will eliminate all hand contact with the tap surface.

Recommendation 3: There is also no evidence of an adequate supply of hand wash soap near the washing basin. The installation of dispensers with soap is recommended. A schedule of regular inspection and refilling should be implemented.

Recommendation 4: Some workers hang their hard hats and respiratory protection (FFP2 mask) on hooks located just outside the tea room (next to the door). However, this is part of the production area where contamination is likely to occur. It is recommended that these hooks be placed in a non-production area or its use be discontinued.

Recommendation 5: The door between the tea room and production area needs to be opened manually, but closes with a recoil system. Opening it requires physical contact with the door, usually the hands. It is recommended that an automatic door system must be installed or if that is not possible that the door surface is cleaned frequently according to a cleaning schedule.

Recommendation 6: It was observed that although workers are frequently reminded of the importance of personal hygiene (i.e. washing hands) through signs and verbally (during health and safety talks), very few workers actually do wash their hands before entering the tea room during breaks. It is recommended that the employer take the necessary steps to ensure that personal hygiene habits are established and enforced.

Recommendation 7: The exterior surface of the lid of the bin in which used/disposed gloves are placed appears very dirty and is most probably also contaminated. By lifting the lid with unprotected hands, contamination is most likely. It is recommended that a foot-operated pedal system be installed to lift the lid and that the exterior surface of the bin be cleaned frequently according to a cleaning schedule.

Recommendation 8: Personal lockers are located in the tea room. It was observed that contaminated hard hats were sometimes placed in the lockers with food (lunch). It is also evident that the door surfaces of the lockers have an exceptionally dirty appearance. It is recommended that the employer prohibit the storage of hard hats in lockers and that lockers be cleaned frequently according to a cleaning schedule.

Recommendation 9: Cleaning services are outsourced to a contractor. Although a cleaning schedule of the tea room exists, it is recommended that it is revised to be more frequent and that it includes surface areas such as locker doors, doors and door handles.

Recommendation 10: The handing in of a dirty overall after taking a shower in the change house creates an additional source of contamination by handling contaminated clothing. The collection bins used to collect dirty overalls should be placed in a position that will allow workers to place the overalls in it before taking a shower.

Recommendation 11: Up to three different types of gloves are currently worn in order to prevent cuts, with little if any chemical protection provided against the sulphuric acid electrolyte solution. It is understood the cotton liner worn beneath the “whizard” glove functions solely to enhance the lifetime of the “whizard” glove. It is recommended that at least one glove should be selected in order to provide adequate chemical protection.

Recommendation 12: Most workers preferred not to wear the cotton liner beneath the “whizard” glove. The “whizard” glove is only replaced when damaged, while the liner glove is replaced daily. Due to the usage over more than one shift without using the liner glove, the risk of skin contamination with nickel will be much higher. Wearing of the liner glove should be encouraged or wearing it must become compulsory.

Recommendation 13: It was observed that some workers remove protective gloves incorrectly, thereby contaminating their hands unnecessarily. Information and training sessions should be scheduled to illustrate the correct removal of protective gloves.

Recommendation 14: It is recommended that an emollient maintenance cream (moisturising lotion) be applied on the skin after completion of a shift (post-shower), to restore the hydration levels of the skin. After implementation and use, the hydration and TEWL indices should be re-evaluated to investigate whether the skin condition actually improved. The application of such creams during the shift is not recommended, as it may entrap contaminants on the skin if washing is inadequate. It has been proven that a barrier cream containing DTPA (diethylenetriaminepenta-acetic acid) as chelator can prevent contact allergic reactions to metals, including nickel (Wöhrl *et al.*, 2001). However, the use of barrier (protective) creams when wearing protective gloves is not recommended (De Craecker *et al.*, 2008).

Recommendation 15: The use of a simple colorimetric test for nickel on skin or other surfaces is also recommended to do "spot tests" on washed hands and cleaned surfaces. The fact that results are instantaneous also makes it an invaluable education and training tool. This test kit (Allertest™ Ni) can be purchased from Allerderm (http://www.allerderm.com). A similar test kit can also be purchased from SKC Inc. It can also be prepared by making a 0.8 – 1% solution of dimethylglyoxime in pure ethanol (solution A) and a 10% ammonium hydroxide solution (solution B). It is recommended that a moist wipe (i.e. Ghostwipe™) is used to wipe the skin or surface. After wiping the skin or surface, a few drops of solution A, followed by solution B are applied to the exposed part of the wipe. If nickel is present, a strawberry-red color will be observed after approximately 30 seconds. This is due to nickel forming a complex with dimethylglyxome, which becomes alkaline in the presence of ammonium hydroxide and turns a strawberry-red color.

8.2.2 Cobalt plant: Article III

Recommendation 1: The hand wash basin is located in a kitchen area next to the control room. The one hand wash basin is considered to be adequate due to the small number of workers per shift. However, the location thereof in an area where food and drink is present is not recommended. It is thus recommended that the hand wash basin should be placed outside the kitchen area, as close as possible to the door separating the control room and production area.

Recommendation 2: Identical to Recommendation 2 in Section 8.2.1.

Recommendation 3: The door between the control room and production area needs to be opened manually, but closes with a recoil system. Opening it requires physical contact with the door, usually the hands. It is recommended that an automatic door system be installed or if that is not possible that the door surface is cleaned frequently.

Recommendation 4: It was observed that very few workers actually do wash their hands. It is recommended that the importance of personal hygiene should be frequently emphasised during health and safety meetings. A sign board, with a clear instruction to wash hands regularly, could be placed on the door between the production area and control room.

Recommendation 5: Cleaning services are outsourced to a contractor. The floor of the control room and adjacent kitchen area are washed every day. Surface sampling indicated that table surfaces in the kitchen area are clean, but that cobalt and nickel is present on computer keyboards and table surfaces in the control room. It is recommended that table surfaces and computer keyboards be cleaned on a daily basis.

Recommendation 6: Several health and safety aspects of concern have been identified by the mining company. As part of their health and safety awareness campaign they have formulated five of these aspects into "platinum rules". One of these rules encourages the use of hand-rails (most commonly found near uneven walkways, stairs and staircases). Surface sampling results indicated very high levels of cobalt and nickel contamination on these hand-rails in the cobalt plant. Access to and from the cobalt plant and its control room necessitates the use of staircases and thus the hand-rails. It is recommended that these hand-rails should be cleaned frequently in order to reduce contamination from this source.

Recommendation 7: Identical to Recommendation 13 of Section 8.2.1.

Recommendation 8: Identical to Recommendation 14 of Section 8.2.1.

Recommendation 9: Identical to Recommendation 15 of Section 8.2.1. For the colorimetric testing of cobalt, Thyssen *et al.* (2010) describes the development and use of disodium-1-nitroso-2-naphthol-3,6-disulfonate in a spot test.

8.2.3 Skin and sensitisation notations: Article IV

The Department of Labour as custodians of the Occupational Health and Safety Act (Act 85 of 1993) and Regulations, including the RHCS, has indicated that an overall review of the Act and its Regulations will commence later in the year (2010). At present the status of the Mine Health and Safety Act, which falls under the Department of Mineral Resources, is not known. The following recommendations will be made:

Recommendation 1: Development and implementation of a strategy which will ensure frequent revision of assignment of skin and sensitisation notations accompanied by accessible supporting documentation.

Recommendation 2: Adoption of the NIOSH skin criteria for use in South Africa is recommended. It is highly unlikely that either of the Departments have the resources or capacity to develop their own criteria.

Recommendation 3: It is recommended that all sensitisers (including nickel and cobalt), irrespective of the route of exposure, should be acknowledged and incorporated in the RHCS and MHSR and other legislation.

Recommendation 4: The development of multiple sensitisation notation criteria whereby the route of exposure, i.e. respiratory (SEN:RES) and skin (SEN:SK) or a combination thereof (SEN:RES/SK) for inclusion in the RHCS and MHSR is also recommended.

8.2.4 Comments on the NiPERA protocol

The Nickel Producers Environmental Research Association (NiPERA) protocol for measuring workplace dermal exposure to metal particles is based on the methodology of Hughson *et al.* (2010) (Adriana Oller, NiPERA, personal communication). The protocol as such was not published in the public domain and was distributed only to associated members. The sampling strategy employed in this thesis was developed without prior knowledge of the NiPERA protocol. This protocol is comprehensive and may in full be applied, but after completion of this thesis and experience gained from it, a few comments on it are justified:

- The protocol states that circular templates with a 25 cm^2 aperture should be used for all sampling. In practice it is easier to manufacture a circular template, but it is difficult to establish a repeatable wiping pattern on a circular shape. For Articles II and III, rectangular templates were manufactured from acetate sheets, with a 2.5 x 4 cm rectangle (10 cm^2) cut out with a ruler and scalpel. Sampling large uneven surfaces such as the side of the neck with a 25 cm^2 (5.64 cm diameter) template may prove to be very challenging. However, a smaller sampling area should be used cautiously as it assumes uniform distribution of the contaminant.

- No samples are collected before the shift. This is a limitation of the protocol as it makes an assumption of no exposure before the shift, contrary to results reported in Article II and III as well as by Day *et al.* (2009).

- The protocol states that samples should be collected three times during a shift, i.e. before breaks and at the end of the shift. The shift structure should determine the intervals of sampling collection as well as the aims of the sampling. In most cases, rest breaks within a shift are not spaced out evenly. This creates some longer shift sessions than others. Also, it does not seem logical to average the three different samples collected to obtain an average result. If the intervals between sampling are of unequal duration, exposure may not be homogenous throughout the shift. However, if the aim is to quantify dermal exposure whilst performing specific tasks, these sampling intervals, are irrelevant.

- The number of samples collected and the cost of subsequent analysis suggested by the protocol is a potential limiting factor. Twenty one samples are collected from each worker (separate samples for the left and right palms, back of hands and forearms), but they are pooled together for analysis. Twelve samples and a field blank amounts to an analysis cost of R1482.00 per worker per shift (analysis cost is currently R114.00 incl. VAT/sample). However, this excludes any sampling prior to the start of the shift to establish any background contamination. If this is also to be incorporated, a total of 30 samples and a blank must be collected for each worker at an analysis cost of R2166.00 (19 samples). Pooled samples, referring to pooling separate wipes together before analysis, may require the use of more chemicals during sample preparation and thus lead to increased analysis cost. If a budget limits the number of samples, priority must be given to sampling of the anatomical areas most likely to be contaminated.

- The protocol was developed by making use of Jeyes “Sticky Fingers” wet-wipes. However, these wipes are only available in the United Kingdom. Also, these wipes are not individually packed and upon opening, the contents carry the risk of being contaminated and more importantly, of losing its moisture which will influence recovery efficiency. The only suitable wipes commercially available in South Africa, are Ghostwipes^{TM} (SKC, part-number 225-2414 for 200 and 225-2413 for 1000). These wipes are distributed by SKC, a global company associated with Occupational Hygiene.

- If samples are not pooled, smaller vials (instead of 250 ml) may be used. The purchase of sterile vials will eliminate the washing of vials before use. Washing a collection vial may also be a source of contamination.

- The recovery efficiency of the operator can also be established as described by the protocol. This is of importance if more than one operator collects the samples.

8.3 Limitations and future studies

In hindsight, several limitations related to assessment of dermal exposure to nickel and/or cobalt and skin condition have been identified:

- The absence of non-exposed control subjects/workers in Article II and III. The general population are frequently exposed to very low levels of nickel through contact with consumer products containing nickel. Liden *et al.* (2008) reported background levels of nickel on the skin ranging between 0.011 and 0.037 μg cm^{-2} for the index finger, and 0.003 to 0.016 μg cm^{-2} for the palm of the hand. Hughson *et al.* (2010) reported a mean nickel background level of 0.048 μg cm^{-2} for the palm of the hand. Inclusion of control subjects would have allowed subtraction of this background environmental exposure. Furthermore, a control group would have enabled additional comparison of skin condition (skin hydration, TEWL and skin surface pH) between the exposed group and control group.

- Apart from the skin condition measurements, skin condition was assessed by making use of a simple questionnaire. However, no clinical examination occurred. Collaboration with a dermatologist to conduct skin examinations on workers and to review medical records of workers could be beneficial in diagnosing skin conditions.

- Inclusion of biological monitoring (urine samples) concurrently with personal air exposure sampling and dermal exposure sampling could have highlighted the contribution of each route of exposure.

Inclusion of the following samples in future projects could further explain dermal exposure levels reported in this thesis:

- Surface sampling of hard hat harnesses (or inside of hard hat) and inside surfaces of protective gloves in order to establish possible levels of contamination with nickel and/or cobalt.

- Sampling and analysis of washed overalls to establish if they are contaminant free and whether overalls contribute to the levels of nickel measured on the skin before shifts.

- Wipe sampling around the peri-oral region to determine the skin loading of nickel and/or cobalt in the proximity of the mouth and, therefore, the ingestion potential.

A future study could be the re-assessment of dermal exposure to nickel at the electro-winning plant after selection and implementation of a chemical resistant glove. In addition, a re-assessment of skin

condition (hydration and TEWL) could be done after introduction of skin moisturisers in order to establish whether its use leads to improved skin condition.

Also, the potential influence of sulphuric acid vapour on skin surface pH could be investigated in the electro-winning plant

Finally, the potential to assess dermal exposure of refinery workers to other platinum group metals, many of which are known sensitisers, has been identified and initiatives are underway to commence with these assessment in the near future.

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occupational health SOUTHERN AFRICA

24 June, 2010

Mr. Johan du Plessis,
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Annexure B: Dalgard skin questionnaire

The Dalgard questionnaire including translation into Setswana:

During the last week, have you had any of the following complaints?
Mo bekeng e e fetileng, a o kile wa nna le ngwe ya dingongorego tse?

	No Nnyaa.	**Yes, a little** Ee. Go le gonnye.	**Yes, quite a lot** Ee. Gantsi.	**Yes, very much** Ee. Gantsi thata.
1. Itchy skin Go babelwa ga letlalo				
2. Dry/sore rash Boswata bo bo omeletseng/botlhoko				
3. Scaly skin Letlalo le le obogang				
4. Itchy rash on your hands Boswata bo bo babelang mo diatleng				
5. Pimples Dipeise				
6. Other rashes on your face Boswata mo sefatlhegong				
7. Warts Diso/dokgoto				
8. Troublesome sweating Go fufulelwa thata				
9. Loss of hair Go wa ga moriri				
10. Other skin problems Mathata a mangwe a letlalo				

If yes, when did the skin problem start? Mark one answer.
Fa karabo ya gago ele ee, bothata jwa letlalo bo simolotse leng? Ka kopo, tshwaya karabo e le ngwe.

During the last week Beke ee fetileng	
During the last month Kgwedi ee fetileng	
1-6 months ago Kgwedi ele ngwe go tse thataro (1-6)	
More than 6 months ago Go feta dikgwedi dile 6 tse di fetileng	