Assessment of the occupational exposure to cobalt at a base metal refinery

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Preface

This mini-dissertation is written for the partial fulfilment of the Masters degree in Occupational Hygiene at the North-West University, Potchefstroom Campus. The mini-dissertation is written in article format. Throughout, the reference style is in accordance with the Annals of Occupational Hygiene journal's requirements. References are given in alphabetical order at the end of each chapter using the Vancouver Style of abbreviation and punctuation.

Author's Contributions

The following Table reflects the contribution of each researcher that was part of this mini-dissertation:

Name	Designation	Contribution
Mrs A de Jager	MSc student	• Proposal and planning of study • Proposal and briefing of employees • Data collection and interpretation • Compilation of mini-dissertation
Prof JL du Plessis	Supervisor	• Assisted in the proposal and planning of study • Approval of proposal • Professional input and recommendations • Review of mini-dissertation
Prof FC Eloff	Co-supervisor	• Assisted with planning of study • Approval of proposal • Professional input and recommendations • Review of mini-dissertation

The following is a statement of the co-authors confirming their individual role in the study:

I declare that I have approved the article and that my role in the study, as indicated above, is representative of my actual contribution and that I hereby give my consent that it may be published as part of Anri de Jager's MSc mini-dissertation.

Prof JL du Plessis

Prof FC Eloff

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- My husband, for his moral support and never ending encouragement and understanding throughout this period.
- All the employees who enthusiastically co-operated in the physical data collection/tests that was required of them.

List of abbreviations

ACD	Allergic Contact Dermatitis
ACGIH	American Conference of Governmental Industrial Hygienists
AD	Aerodynamic Diameter
ANOVA	Analysis of Variance
ATSDR	Agency for Toxic Substances and Disease Registry
BEI	Biological Exposure Index
BMR	Base Metal Refinery
°C	Degrees Celsius
CDI	Cobalt Development Institute
CoAsS	Cobaltite
$CoSO_4.7H_2O$	Cobalt (II) Sulphate Heptahydrate
DNA	Deoxyribonucleic Acid
Etc	Et cetera
GFAAS	Graphite Furnace Atomic Absorption Spectrometry
GM	Geometric Mean
GSD	Geometric Standard Deviation
IARC	International Agency for Research on Cancer
IgE	Immunoglobulin E
IOM	Institute of Occupational Medicine
ℓ/min	Litres per minute
MCP	Magnetic Concentrate Plant
m^2	Square metres

mg/m^3	Milligrams per cubic metres
NCM	Nickel Copper Matte
NIOSH	National Institute for Occupational Safety and Health
NMF	Natural Moisturising Factor
NTP	National Toxicological Programme
OEL	Occupational Exposure Limit
OMP	Occupational Medical Practitioner
%	Percentage
PGMs	Platinum Group Metals
PMR	Precious Metals Refinery
PPE	Personal Protective Equipment
SC	Stratum Corneum
TEWL	Transepidermal Water Loss
TLV	Threshold Limit Value
TWA	Time Weighted Average
$\mu g/cm^2$	Microgram per square centimetres
µg/g Cr	Microgram per gram Creatinine
µg/ℓ	Microgram per litre
UV	Ultra Violet
CM	Concentrate Matte
WHO	World Health Organisation

Abstract

Title: Assessment of the occupational exposure to cobalt at a base metal refinery.

Objectives: The objectives for this study were (i) to assess the respiratory exposure of base metal refinery workers to cobalt sulphate; (ii) to assess the dermal exposure of these workers to cobalt sulphate; (iii) to assess the skin barrier function by means of TEWL, skin hydration and skin surface pH; (iv) to assess workers' urine cobalt concentration by means of biological monitoring and; (v) to determine the contribution of each exposure route to the total urine content.

Methods: The study was conducted at a base metal refinery where workers stationed in a Cobalt plant (20 workers) and Packaging plant (5 workers) are potentially exposed to soluble cobalt sulphate through respiratory and dermal exposure routes. Evaluation of the respiratory exposure was quantified using the Institute of Occupational Medicine (IOM) aerosol sampler. Evaluation of the dermal exposure included quantification of the cobalt deposition on the skin using Ghostwipes™ as a removal method, while TEWL, skin hydration and pH measurements were used to determine the change in skin barrier function. Dermal measurements were done on four different anatomical areas (forearm, wrist, palm of hand and back of hand) before, during and after the working shift. Evaluation of the cobalt content in the urine of employees was included to evaluate the exposure through all exposure routes (respiratory and dermal).

Results and Discussion: Occupational exposure to cobalt at a base metal refinery was detected through the respiratory and dermal routes of exposure. High inhalable airborne exposures above the Occupational Exposure Limit - Time Weighted Average (OEL-TWA) were noted for several workers in both the Cobalt and Packaging plant of the base metal refinery. Respirable fractions only contributed a small fraction of the total airborne exposure to cobalt. Detectable levels of cobalt were found on the skin of exposed workers in both the Cobalt and Packaging plant with geometric means ranging between 0.104 µg/cm^2 on the back of hand and 77.600 µg/cm^2 on the wrist. The majority of measurements indicated an increase in TEWL percentage changes from the beginning to the end of the shift, with a

decrease being reported in all skin hydration measurements, and pH indicating high variability between the Cobalt and Packaging plant. Biological monitoring data indicated baseline urine levels above the Biological Exposure Index (BEI) of 15 µg Co/g Creatinine in five out of the 12 workers in the Cobalt plant. The mean urine cobalt concentration in Cobalt plant workers decreased slightly from a baseline measurement of 17.83 µg Co/g Creatinine to 12.37 µg Co/g Creatinine on day 5. Workers' urine levels in the Packaging plant however indicated cobalt concentrations of approximately three times lower than the recommended BEI, with levels ranging between a baseline measurement of 2.5 µg Co/g Creatinine and 6.6 µg Co/g Creatinine on day 5. Pair wise correlations indicated significant strong positive correlations between dermal exposure and biological monitoring (change in urine cobalt concentration between Day 3 and the Baseline) in the Cobalt plant and the Cobalt and Packaging plants combined.

Conclusion: Refinery workers are exposed to cobalt sulphate (liquid solution and cobalt sulphate crystals) through the respiratory and dermal routes of exposure in both the Cobalt and Packaging plant of the base metal refinery, of which only dermal exposure significantly correlated with the total urine content of the workers. Changes in the skin barrier function also indicated that the skin integrity was compromised.

Keywords: respiratory exposure, dermal exposure, barrier function, transepidermal water loss, skin hydration, skin surface pH, biological monitoring, cobalt sulphate, refinery, occupational health risk

Opsomming

Titel: Bepaling van die beroepsblootstellingsvlakke aan kobalt by ’n basis metaal raffinadery.

Doelwitte: Die doelwitte van hierdie navorsingstudie was (i) om die respiratoriese blootstelling van raffinadery-werkers aan kobaltsulfaat te bepaal; (ii) om die dermale blootstelling van die werkers aan kobaltsulfaat te bepaal; (iii) om die velgrensfunksie te ondersoek deur middel van transepidermale waterverlies, velhidrasie en vel oppervlak-pH, (iv) om die werkers se urine-kobaltkonsentrasie deur middel van biologiese monitering vas te stel; en (v) om die totale bydrae van elke blootstellingsroete tot die totale kobalt-urienvlakke te bepaal.

Metodes: Die voorgestelde studie is uitgevoer by ’n raffinadery waar werkers wat gestasioneer is in ‘n Kobalt-area (20 werkers) en ‘n Verpakkingsarea (5 werkers), moontlik blootgestel word aan kobaltsulfaat deur middel van respiratoriese en dermale blootstellingsroetes. Evaluering van die respiratoriese blootstelling is gekwantifiseer deur gebruik te maak van die Instituut vir Beropesmedisyne (IOM) aerosolfilter. Evaluering van die dermale blootstelling het die kwantifisering van die kobalt-neerlegging op die vel met behulp van Ghostwipes™ behels as verwyderingsmetode, waar transepidermale waterverlies, velhidrasie en pH-waardes gemeet is om die verandering in velgrensfunksie te evalueer. Dermale lesings is geneem op vier verskillende anatomiese areas (voorarm, pols, palm van die hand en agterkant van die hand) voor, gedurende en aan die einde van die werkskof. Evaluering van die kobalt-inhoud in die uriene van die werkers is ingesluit om alle moontlike blootstellingsroetes in ag te neem (respiratories en dermaal).

Resultate en Bespreking: Beroepsblootstelling aan kobalt in ‘n basis metal raffinadery vind deur die respiratoriese en dermale roetes van blootstelling plaas. Oormatige blootstelling aan inasembare kobalt bo die beroepsblootstellingsdrempel – tyd geweegde gemmideld is waargeneem in sommige werkers in die Kobalt-area, sowel as die Verpakkingsarea van die raffinadery. Respireerbare fraksies het slegs ‘n klein bydrae gelewer tot die totale blootstelling aan kobaltsulfaat. Waarneembare vlakke van kobalt is gevind op die vel van blootgestelde werkers in beide die Kobalt-

en Verpakkingsareas met waardes wat wissel tussen 0.104 µg/cm^2 op die agterkant van die hand en 77.600 µg/cm^2 op die gewrig. Die meerderheid van die metinge het getoon dat transepidermale waterverlies-persentasieveranderinge van die begin tot die einde van die skof toegeneem het, terwyl ‘n afname in velhidrasiedata gerapporteer is. Die pH het egter hoogvarieerbare data tussen die werkers in die Kobalt- en Verpakkingsareas aangetoon. Biologiese moniteringsdata het aangetoon dat die basislyn urine-kobaltmonsters wat geneem is, in 5 van die 12 werkers oor die Beroeps Blootstellings Indeks (BBI) van 15 µg Co/g Kreatinien in die Kobaltarea was. Die gemiddelde urien kobalt konsentrasie van werkers in die Kobalt area het effens afgeneem van ‘n basislyn lesing van 17.83 µg Co/g Kreatinien tot 12.37 µg Co/g Kreatinien op dag 5. Die Verpakkingsarea het egter resultate opgelewer wat ongeveer drie keer laer as die voorgestelde BBI was, met lesings wat varieer tussen ‘n basislyn lesing van 2.5 µg Co/g Kreatinien en 6.6 µg Co/g Kreatinien op dag 5. Gepaarde korrelasies het betekenisvolle sterk positiewe korrelasie getoon tussen gemiddelde dermale blootstelling en biologiese monitering (verandering in kobaltkonsentrasie tussen Dag 3 en die Basis) in beide die Kobalt area en die Kobalt- en Verpakkingsareas gekombineerd.

Gevolgtrekking: Raffinaderywerkers word blootgestel aan kobaltsulfaat (vloeistof en kobaltsulfaatkristalle) deur die respiratoriese en dermale blootstellingsroetes in beide die Kobaltarea en die Verpakkingsarea van die raffinadery, waarvan slegs dermale blootstelling betekenisvolle verskille aangewys het, saam met die biologiese moniteringsdata van die betrokke werkers. Veranderinge in die velgrensfunksie het ook aangedui dat die vel integriteit negatief beïnvloed is.

Sleutelwoorde: respiratoriese blootstelling, dermale blootstelling, velgrensfunksie, transepidermale waterverlies, velhidrasie, vel oppervlak pH, biologiese monitering, kobaltsulfaat, raffinadery, beroepsgesondheidsrisiko.

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CHAPTER 1: INTRODUCTION, OBJECTIVES AND HYPOTHESIS

1.1 Introduction

Cobalt can be seen as a natural earth element which is essential in trace amounts for human life for the key role it plays in the formation of Vitamin B_{12} (Barceloux, 1999; Garner, 2004; Permenter *et al*., 2013). Occupational exposure to excessive levels of cobalt can however cause adverse health effects through inhalation, skin contact and ingestion (ATSDR, 2004).

South Africa has a thriving mining industry with a firm base in technology and knowledge of cobalt refining processes. A Base Metal Refinery (BMR) is part of a large integrated mining and metallurgical complex that treats very little Platinum Group Metals (PGMs). Concentrated Matte (CM) is fed into a Magnetic Concentrate Plant (MCP) where it goes through three stages of crushing and milling. The fine CM then undergoes a magnetic process of leaching and filtration to separate the PGMs from the base metals. PGMs are separated and sent to a magnetic alloy fraction that is then sent to a precious metal refinery for further refining. A non-magnetic fraction (nickel, copper and cobalt) is then transferred to the BMR where the cobalt solution is purified, extracted and crystallised in a Cobalt plant where after it is packed in a Packaging plant section for vendor shipment (Hofirek and Halton, 1990).

Experimental studies have concluded that inhalation of cobalt may cause significant deposition in the lungs that can be associated with acute symptoms such as wheezing, coughing and shortness of breath (Swennen *et al*., 1993). Cobalt sulphate and other soluble cobalt (II) salts are also classified by the International Agency for Research on Cancer (IARC) as possible (Group 2B) human carcinogens. The IARC also specified that an increased lung cancer risk exists in subjects exposed to cobalt sulphate in the long term (IARC, 2006).

Occupational settings like refineries have been classified as one of the main culprits in terms of exposing their workers to cobalt, with the main route of exposure being through inhalation and to a lesser extent, ingestion (Lison *et al*.,1994; Cherrie *et al*., 2006). Another important route of exposure that was not acknowledged in the past is skin exposure. This was driven by the traditional belief that the skin has an

impermeable surface, causing it to be overlooked when evaluating the impact of chemicals on health (Semple, 2004). Studies have however proven that many substances, including cobalt, have the ability to penetrate the skin and cause adverse health effects (Fenske, 2000; Sartorelli, 2002; Trommer and Neubert, 2006; Larese Filon *et al*., 2009).

The Mine Health and Safety Act (no. 29 of 1996) of South Africa has established an 8-hour occupational respiratory exposure limit (TWA-OEL) of 0.05 mg/m^3 for cobalt and its compounds. In contrast, there are no occupational exposure limits for skin exposure. The only legal recommendation regarding dermal exposure is skin notations that merely serve as a warning sign. Various authorities have instituted skin notations for a variety of substances, but none assigned to cobalt (Sartorelli, 2002; Semple, 2004).

Although literature on respiratory exposure of workers associated with the refining of metals such as cobalt is well defined and documented, there is limited information available on skin exposure to contact allergens in terms of the deposition of cobalt on the skin and ultimately how cobalt is absorbed in the body (Liden *et al*., 2006; Julander *et al*., 2010; Du Plessis *et al*., 2013). Previous studies have however concluded that skin exposure to cobalt may cause allergic contact dermatitis which can result in high costs of occupational skin disease, both for the worker in terms of disability and for the responsible company in terms of days lost and medical/compensation expenses (Shirakawa *et al*., 1990; Percival *et al*., 1995; Filon *et al*., 2004; Julander *et al*., 2009).

Many factors can influence the rate at which cobalt is absorbed through the skin. These factors include the anatomical site, occlusion, temperature and the presence of other substances on the skin to mention a few (Semple, 2004). The integrity of the stratum corneum also plays a vital role in the uptake of chemicals through the skin (Semple, 2004). The stratum corneum can be defined as the primary skin barrier that has a flexible character, but when it is damaged or dehydrated it becomes hard and brittle (Proksch *et al*., 2008; Mündlein *et al*., 2008; Kezic and Nielsen, 2009). This not only makes it easier for chemicals to penetrate through the stratum corneum but also facilitates the uptake of chemicals into the bloodstream and multiple organs where they may be deposited, metabolised, excreted or exert systemic biological effects

(Liu *et al*., 2008; HSE, 2009; Du Plessis *et al*., 2010). Local effects can also occur and are limited to the skin itself. Allergic contact dermatitis (ACD) can be defined as an immunological response to a sensitising agent that may develop over time. This occurs due to xenobiotic chemicals that penetrate the skin, causing a chemical reaction with self-proteins and finally resulting in a hapten-specific immune response. Once a person has been sensitised, it only requires minimal re-exposure to trigger a reaction. When this happens, the only remedy is to remove the person from exposure, thus highlighting the importance of prevention rather than cure (Gober and Gaspari, 2008; HSE, 2009).

Dermal exposure to cobalt can be accurately assessed in most instances by making use of removal methods. Removal techniques give a clear indication of the mass of contaminant on a workers' skin at a particular point in time (Semple, 2004). Skin hydration, transepidermal water loss (TEWL) and skin surface pH are known parameters that can be used to assess skin barrier function (Du Plessis *et al*., 2010). TEWL represents the amount of water (excluding sweat) that diffuses through the stratum corneum between the dermal layers of the epidermis and the atmosphere (Fluhr *et al*., 2006; Imhof *et al*., 2009), while skin hydration indicates the level of moisture present in the stratum corneum (Rawlings, 2006). An optimal skin surface pH gives an indication of healthy skin barrier function and stratum corneum integrity (Lambers *et al*., 2006).

Due to the multiple routes of exposure associated with cobalt, biological monitoring has gained increasing attention as a means of accurately assessing the total exposure to cobalt (Marek and Malgorzata, 2005). Biological monitoring is thus a measurement of the total uptake of a chemical by all routes. Cobalt is not considered to have a cumulative effect, and is mainly excreted in the urine. Urine samples have thus been identified as the best biological matrix to determine the total absorption of cobalt (Lauwerys and Lison, 1994). The elimination of urine cobalt content can be explained by a rapid phase that lasts for a few days, contributing to 80-90% elimination of the absorbed dose, followed by a second slower phase that can last up to two years or more (Lison *et al*., 1994; Barceloux, 1999). The American Conference of Governmental Industrial Hygienists (ACGIH) has established a biological exposure index (BEI) of 15 µg/ℓ for insoluble forms of cobalt (ACGIH, 2013).

Exposure to cobalt sulphate in the workplace can thus be assessed by measuring the presence of cobalt in the air that the workers breathe in, or by measuring cobalt deposition on their skin. However, this does not indicate the internal dose as a result of skin absorption, inhalation and ingestion. This is why biological monitoring is recommended to determine the total uptake of cobalt through all possible routes of exposure.

1.2 Research aims and objectives

The general aim of this study was to assess the occupational exposure of workers to cobalt sulphate at a base metal refinery.

More specifically this study had the following objectives:

- To assess the respiratory exposure of refinery workers to cobalt sulphate;
- to assess the dermal exposure of refinery workers to cobalt by quantifying cobalt deposition on the skin;
- to assess the skin barrier function by means of TEWL, skin hydration and skin surface pH;
- to assess the workers' urine cobalt concentration by means of biological monitoring; and
- to correlate respiratory exposure, dermal exposure and biological monitoring results with each other in order to determine the contribution of cobalt absorption via both routes of exposure.

1.3 Hypothesis

1. Workers in a Cobalt plant of a base metal refinery are exposed to cobalt sulphate through the dermal route of exposure, and based on previous literature during the subsequent packaging thereof in a Packaging plant.

2. Workers at a base metal refinery are exposed to cobalt sulphate through the respiratory and dermal routes of exposure, which can be positively correlated with the workers' total urine cobalt concentration.

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CHAPTER 2: LITERATURE STUDY

2.1 Introduction

Metals play a vital role in human physiology, and cobalt is no exception. Cobalt is a nutritionally essential trace element that forms the active centre of coenzymes called cobalamin in vitamin B_{12}. Vitamin B_{12} contains approximately 4% cobalt and can be defined as a water soluble vitamin that plays a vital role in the formation of red blood cells and the normal functioning of the brain and central nervous system (Lauwerys and Lison, 1994; Liu *et al*., 2008; Permenter *et al*., 2013).

Excessive exposure to cobalt can however be harmful to human health, causing it to be a concern in occupational settings like refineries. South Africa has a thriving mining industry with a firm base in technology and knowledge of cobalt refining processes. Cobalt sulphate is mainly produced as a by-product of Platinum Group Metals (PGMs), nickel and copper refining. Refineries have thus been classified as the main culprit in terms of exposing workers to cobalt salts, its metal oxides or to mixed compounds of cobalt dusts (Hofirek and Halton, 1990; Lison *et al*., 1994).

Exposure in the workplace can occur through multiple exposure routes, with the respiratory route traditionally seen as the main target organ in occupational settings like refineries (Swennen *et al*., 1993). Recent studies have however drawn more attention to the dermal route of exposure as many chemicals also have the ability to penetrate the skin, causing local and systemic effects (Fenske, 2000; Sartorelli, 2002; Semple, 2004; Trommer and Neubert, 2006).

This literature study will focus on the physical and chemical properties, sources and different routes of exposure to cobalt sulphate, as well as the physiology associated with skin absorption (skin barrier function) and inhalation through the respiratory tract, the specific health effects associated with each route of exposure and the total uptake of cobalt via all routes of exposure.

2.2 Physical and chemical properties of cobalt and its compounds

Cobalt is a relatively rare element that is widely distributed in the earth's crust (Barceloux, 1999). Cobalt is one of three ferromagnetic elements that possess magnetic properties similar to nickel and iron. Cobalt has an atomic number of 27 and an atomic weight of 58.9332. Cobalt is also known for its transition properties where its crystal structure is presented as close-packed hexagonal at room temperature and face centred cubic above 417˚C (Barceloux, 1999; CDI, 2013; NPI, 2013).

Cobalt exists in a wide variety of oxidation states. The two most prevalent valence states of cobalt are cobaltous (II) and cobaltic (III), with the former being the most common valence used in the chemical industry due to its stability in water (Barceloux, 1999; WHO, 2006; Kim *et al*., 2006; NPI, 2013). The divalent state of cobalt salt is known as cobalt sulphate ($CoSO_4$), with the most common form being the hydrate ($CoSO_4 \cdot 7H_2O$).

2.3 Sources of cobalt and its compounds

2.3.1 Environmental sources

Cobalt is a metal that occurs both naturally and anthropogenically in the environment (WHO, 2006). In nature cobalt is usually found in chemically combined forms of arsenides, oxides and sulphides (Barceloux, 1999; NPI, 2013). Small amounts can thus be found in most rocks, soil, water, plants, volcanoes, forest fires and animals (ATSDR, 2004; WHO, 2006). Anthropogenic sources of cobalt are primarily found in the form of oxides. The main source is the mining and processing of cobalt bearing ores known as cobaltite (CoAsS) and other sources including phosphate fertilizers and the burning of fossil fuels (ATSDR, 2004; WHO, 2006). Cobalt contributes to approximately 0.0025% of the earth's ores. These small amounts of cobalt are usually not mined alone and are generally recovered as by-products of nickel and copper production in the form of cobaltous sulphate. Approximately 44% of cobalt originates from nickel ores, with approximately 30% originating from copper ores (Barceloux, 1999; WHO, 2006).

2.3.2 Essential sources

Cobalt is one of 27 essential elements needed for human life. This oligo-element needs to be absorbed from the diet in very small amounts because the body cannot synthesise cobalt (Lauwerys and Lison, 1994; CDI, 2013). The main function of cobalt (cobalamin) in the human body is the integral part it plays in the formation of Vitamin B_{12} (Garner, 2004). Vitamin B_{12} is a water soluble vitamin that contains approximately 4% cobalt. It plays an important role in the formation of red blood cells and the normal functioning of the brain and nervous system (Lauwerys and Lison, 1994; Liu *et al*., 2008).

In the general population, the main nutritional sources of inorganic cobalt can be linked to many foods and beverages that form part of most individuals' daily diet such as fish, leafy vegetables, fresh cereals, dairy products, beer, cigarettes and in some rare instances drinking water. The estimated intake of cobalt through food and beverages is approximately 5-40 µg/day (Christensen *et al*., 1993; Dabeka and McKenzie, 1995; Barceloux, 1999; WHO, 2006).

2.4 Uses of cobalt

Cobalt has a diverse range of important uses in agricultural and industrial settings. It can be used in the electroplating and electrochemical industries and also acts as a drier for various paints, varnishes and pigments. It is also used as a colouring agent in ceramics and enamels. Some other applications where cobalt is useful, are in the production of magnets and jewellery. Agricultural uses include the use of cobalt as an additive in fertilisers and animal feeds (Lauwerys and Lison, 1994; Budavari *et al*., 1996; Richardson, 2003; Thyssen *et al*., 2009).

2.5 Exposure to cobalt

Occupational settings like refineries are one of the main culprits in terms of exposing their workers to cobalt salts, its metal oxides or to mixed compounds of cobalt dusts. Traditionally, the main route of exposure to cobalt is through inhalation and to a certain extent by ingestion (Lison *et al*., 1994; Cherrie *et al*., 2006). Cobalt is

primarily absorbed from the pulmonary tract (Lauwerys and Lison, 1994). Because of the traditional belief that the skin was almost impermeable to chemical substances, it resulted in the oversight of this important route of exposure when it came to chronic disease and allergy (Swennen *et al*., 1993; Lauwerys and Lison, 1994; Julander, 2014). Recent studies, however, proved that many substances have the ability to penetrate the skin causing systemic and local effects (Fenske, 2000; Sartorelli, 2002; Trommer and Neubert, 2006). A limited number of studies have concluded that, in the workplace, damaged skin negatively compromises the skin barrier function and will ultimately increase the dermal absorption of chemicals, which cannot penetrate intact skin (Larese Filon *et al*., 2009). Dermal exposure can occur through direct contact due to immersion/spillage and through indirect contact with a contaminated surface or object (Scansetti *et al*., 1994).

2.5.1 Respiratory exposure

Cobalt sulphate is a powdery pink substance that can easily become dispersed in air, posing a risk for exposed workers (Eloff *et al*., 2011). Following inhalation, the primary target of exposure is the respiratory tract. This exposure will result in deposition of cobalt in the upper and lower regions of the respiratory tract depending on the size of the particles. Larger cobalt particles will reach the upper respiratory tract where they will undergo mechanical ciliary clearance and transfer to the gastrointestinal tract. Smaller cobalt particles are however known to reach the lower regions of the respiratory tract where they are absorbed and known to cause adverse health effects in several target organs that will be fully explained in the following sections (ATSDR, 2004; WHO, 2006; De Palma *et al*., 2010).

2.5.1.1 The Respiratory System

For better understanding it is important to be familiar with the anatomy and physiology of the respiratory system. The respiratory system is situated in the head, neck and chest and is responsible for gas exchange by supplying oxygen to body tissues and removing carbon dioxide. The respiratory tract can be divided into two sections, namely the upper, and lower respiratory sections. The upper respiratory system, also known as the conducting zone, includes the nasal cavity (nose), oral cavity (mouth), pharynx, epiglottis, larynx, oesophagus, trachea and ends in the bronchial tree. The upper respiratory tract is mainly responsible for conducting air

from the external environment into the lower regions. The lower respiratory system starts at the small subdivisions of the bronchial tree, known as the bronchioles and extends downwards to form the alveoli. The alveoli can be described as millions of very small air pockets with small capillaries/blood vessels and is responsible for gas exchange. The capillaries discharge carbon dioxide back into the alveoli and take up the oxygen from the inhaled air to be transported to the rest of the body via blood (Calder, 2009).

2.5.1.2 Particle deposition and absorption of cobalt

For occupational hygiene purposes it is also important to define inhalable, respirable and thoracic fractions, because different particle sizes cause different health effects in different parts of the respiratory system (WHO, 2005). Inhalable particles can enter the upper respiratory tract and have an aerodynamic diameter of up to 100 µm. Thoracic particles have an aerodynamic diameter of less than 30 µm and can enter the lung airways and gas exchange region. The respirable fraction includes those particles that can reach the alveoli and have an aerodynamic diameter of 7-10 µm (Belle and Stanton, 2007).

The number of particles that are deposited in the respiratory tract depends on the particle size, shape, specific gravity, density and aerodynamic diameter (AD) as well as the volume of contaminated air inhaled. The mechanisms that indicate where deposition will occur include impaction, interception, sedimentation and diffusion (DiNardi, 1998). Impaction can be described as the process where a particle is unable to remain in the current airstream due to the air changing direction, resulting in the particle striking a stationary obstacle directly in its path, and thereby being removed from the air. This is more prominent in the bronchial regions of the lungs. Interception is where a particle is able to remain in the airstream but, due to its dimension (size and shape), strikes a stationary obstacle and is removed from the air. This usually occurs in the small airways. Sedimentation usually occurs when a particle in an airstream is pulled downwards due to gravity until it strikes a stationary obstacle and is removed from the air. Diffusion can be explained by the gradual mixing of two or more substances due to thermal motion until they strike a stationary obstacle and are removed from the air, but this has no relevance to cobalt uptake (Heyder, 2004; Breysse and Lees, 2006).

After deposition of particles in the different regions of the respiratory tract, they will be absorbed into the bloodstream and delivered to organs such as muscle, liver, kidneys, stomach, skin, bladder, brain and lymph nodes. The rate of absorption depends on the solubility of the cobalt compounds in the biological medium (Scansetti *et al*., 1994; Barceloux, 1999). Larger particles that deposit in the upper regions of the respiratory tract will be absorbed through mechanical clearance processes, while smaller particles that deposit in the lower respiratory tract will be dissolved or phagocytised by macrophages (WHO, 2005).

2.5.2 Skin exposure

In the field of occupational health and safety, skin absorption is particularly important in assessing the risk of exposure to toxic substances such as cobalt (Larese Filon *et al*., 2004). Important research has been directed towards exploring the toxicological mechanisms that govern their way through the human skin, but the precise understanding of the process and amount of penetration is partly unresolved. The reason for this can be explained by the failure to account for chemical specification of metals due to the fact that movement through a complex membrane like the skin is chemical and element species dependent. Another reason is the wide margin of variability with regard to the anatomical site and physical condition of the skin. Definite rules that define general skin penetration are thus inconclusive and must be individually determined for every metal species. It is thus evident that a great need exists to accurately assess and interpret the species-specific dermal exposure to cobalt in the workplace by accounting for all exogenous and endogenous factors that could contribute to this wide margin of error involved in the determination of skin penetration (Hostýnek, 2003; Liden *et al*., 2006; WHO, 2006; Julander *et al*., 2010).

2.5.2.1 The anatomy of the skin

The skin, or integument, is defined as the largest and most complex organ of the body that provides a protective barrier between the external and internal environment (Proksch *et al*., 2008). It covers a square surface of 1.5 to 2 m^2, representing approximately 16% of the total body weight. To understand the complexity of the skin and its functions, it is important to explore further into the anatomy of the skin and its many integumentary components. The basic design of

the skin centres around its subdivisions into two major components known as the epidermis and the dermis (McGrath *et al*., 2004).

The epidermis is a constantly self-renewing tissue that consists of the outermost layer of the skin and provides the first barrier of protection from the invasion of chemicals into the body. It is mainly made up of two sets of cells known as the keratinocytic and non-keratinocytic cells (Swanson, 1996; McGrath *et al*., 2004; Samaha, 2010).

The keratinocytes are known to be the major component of the epidermis as they migrate through the different layers of the epidermis, undergoing multiple changes in its structure and composition, and finally producing corneocytes filled with the intracellular protein, called keratin and surrounded by proteins and lipids. It can thus be defined as stratified squamous keratinised epithelium made up of four histological distinct regions (Van Smeden *et al*., 2013).

The stratum corneum can be found on the outside of the skin and consists of multiple layers of flattened cells known as corneocytes that have no nucleus or cytoplasmic organelles. These corneocytes protect the skin against external chemicals and physical stressors as they are in constant contact with the environment. The corneocytes are held together by desmosomes in an intercellular lipid matrix which forms a seal, thus preventing transepidermal water loss and the uptake of unwanted chemicals. This layer contains keratin that is a tough, durable and waterproof protein that is formed within cells of the stratum granulosum just beneath the stratum corneum (McGrath *et al*., 2004).

Keratinocytes in the stratum granulosum contain lamellar bodies that secrete lipids into the intercellular spaces leading to the stratum corneum. These lipids contain filaggrin that is essential for the regulation of homeostasis in the epidermis. Filaggrin can be described as a class of structural proteins that interacts with keratin, contributing to cellular compaction and cross linking of keratin intermediate filaments by trans glutaminases to create a highly insoluble keratin matrix. This matrix plays a vital role in the stratum corneum where it acts as a protein scaffold for the attachment of proteins and lipids that are required for desquamation, consequently maintaining a healthy barrier function and intercellular cohesion within the stratum corneum (Sandilands *et al*., 2009; Hogan *et al*., 2012).

Beneath the stratum granulosum lies the stratum spinosum. The stratum spinosum contains large polygonal cells that are attached to one another by small spines known as desmosomes. The deepest region of the epidermis is called the stratum germinativum and is responsible for supplying the cells to replace those lost at the surface. The movement of the epidermal cells through all these regions is part of a dynamic process that involves cell proliferation, cell differentiation and cell death (Hogan *et al*., 2012).

The non-keratinocytes consists of melanocytes, Langerhans cells and Merkel cells. Melanocytes are known as the pigment producing cells and form a close association with the keratinocytes via their dendrites. These cells are regulated by melanocortin and have the ability to produce and distribute melanin. Another important function of the melanocytes is to protect the hypodermis from the UV rays of the sun by absorbing light. The Langerhans cells are dendritic cells that function as immune surveillance cells where they take up and process antigens to become fully functional antigen-presenting cells. Merkel cells are characterised as dense-core granular dendrites which are loosely arranged and known to function as slow adapting mechanoreceptors for touch (Swanson, 1996; Tsatmali *et al*., 2002; Madison, 2003; McGrath *et al*., 2004; Goldschmidt, 2005; Moll *et al*., 2005; Samaha, 2010).

Undulating ridges known as rete ridges connect the epidermis to the dermis. This vitally important connection is defined as the epidermis-dermis junction that plays an important role in cellular communication, nutrient exchange and absorption. Nutrient exchange is vital for DNA repair processes, new cell production and protection from outside elements and oxidative stress. Without this nutrient exchange, the skin will be more susceptible to premature ageing and damage, allowing for entry of unwanted chemicals (McGrath *et al*., 2004; Bien-etre, 2010).

The dermis is located underneath the epidermis and can be defined as a highly vascular bed of connective tissue that is subdivided into two regions known as the papillary and reticular dermis. The papillary dermis consists of superficial loose connective tissue whereas the reticular dermis contains an extensive layer of collagen and elastic fibres that make up a deeper dense connective tissue. In addition to blood vessels and nerves, it also contains important derivates such as

hair follicles, sebaceous glands and sweat glands (Swanson, 1996; McGrath *et al*., 2004; Samaha, 2010).

The hypodermis is made up of subcutaneous fatty tissue that is located under the skin and provides a cushioning effect against mechanical stressors (McGrath *et al*., 2004; Marieb and Hoehn, 2013).

2.5.2.2 Percutaneous absorption and the skin barrier

Human skin is not a completely impermeable structure. Two main transdermal routes exist and are known as the transappendageal and transepidermal routes. The transappendageal route is also known as the follicular or shunt route and accounts for permeation through the sweat glands and hair follicles. The transepidermal route can further be divided into two micro-pathways known as the intercellular and transcellular pathways. The intercellular route accounts for permeation through the continuous intercellular lipid domains while the transcellular route permeates through the keratinocytes layers. The route of penetration however depends on the physio-chemical properties of the incoming element (Prasanthi and Lakshmi, 2011). Endeavors to define the rules of governing skin penetration for metallic elements have been studied, but still need to be determined separately for each metal species by *in vitro* or *in vivo* assays (Hostýnek, 2003; Larese Filon *et al*., 2009). This experimental variability may be ascribed to differences in the biological material. This is particularly true for the composition of lipid domains in the stratum corneum that causes wide variations in permeability measurements (Loth *et al*., 2000). The movement of metal particles through a biological membrane such as the skin depends on many exogenous factors such as the type of metal, chemical properties, dose, molecular volume, valence, solubility and pH dependence of the chemical. Endogenous factors such as ageing of the skin, gender, race, anatomical sites and oxidation and reduction of xenobiotics in the skin can also influence the absorption of chemicals through the skin (Hostýnek, 2003).

Another vital factor that determines the rate of skin permeability is the condition of the skin. As discussed earlier, the stratum corneum is in direct contact with the external environment and provides a barrier to control the rate at which a chemical is able to penetrate the skin. The stratum corneum also prevents water loss from the skin by means of a hydrophobic extracellular lipid matrix (Hatzis, 1995; Proksch *et*

al., 2008; Kezic and Nielsen, 2009). The stratum corneum has a flexible character that typically contains approximately 10-20% of water, but when it is damaged/dehydrated it becomes hard and brittle (Zhai and Maibach, 2002; Mündlein *et al*., 2008). Overhydration is also associated with disruption of the corneocytes and the stratum corneum lipids (Stone *et al*., 1998). This makes it easy for chemicals to penetrate through the stratum corneum and diffuse into the dermis where they enter the bloodstream and distribute to multiple organs where they may be deposited, metabolized, excreted or exert biological effects (Liu *et al*., 2008). The function of this skin barrier is thus to control and prevent harmful chemicals from entering the human body and causing damage. In occupational settings, a compromised skin barrier is common due to physical and/or chemical damage. Reduced integrity of the skin barrier can not only lead to an increase in dermal absorption of chemicals, but also to the entrance/penetration of larger molecules and allergens into the skin that is associated with the activation of immunological reactions and inflammation. (Proksch *et al*., 2008; Kezic and Nielsen, 2009; Larese Filon *et al*., 2009).

There are various existing methods that can be used to assess the dermal exposure to certain substances. These methods include surrogate skin methods, removal methods and fluorescent tracer methods. Because of the low capital costs, ease of analysis and use and after considering the primary and secondary sources of contact, it can be assumed that a removal method, using skin wipes, is the best method for removal of cobalt from the skin (Fenske, 1993; Brouwer *et al*., 2000; Julander *et al*., 2010).

Skin barrier function can also be determined by assessment of transepidermal water loss (TEWL), skin hydration and the skin surface pH and will be explained in detail in the following section.

2.5.2.3 Transepidermal water loss (TEWL)

Transepidermal water loss (TEWL) represents the amount of water (excluding sweat) that diffuses through the stratum corneum from the dermal layers of the epidermis to the outside atmosphere (Chilcott *et al*., 2002; Imhof *et al*., 2009). Measurements of TEWL are expressed in grams per square meter per hour and can be successfully used for early detection of disturbances in the skin’s protective

barrier function (Zhai and Maibach, 2002; Mundlein *et al*., 2008). Healthy intact skin is mainly associated with high water content (stratum corneum hydration) and low TEWL readings. However, when the skin barrier becomes damaged due to altered integrity of the stratum corneum, the amount of water that evaporates increases resulting in higher levels of TEWL, but the exact mechanism of action is still unresolved (Fluhr *et al*., 2006; Proksch *et al*., 2008; Imhof *et al*. 2009). Many exogenous, endogenous and environmental factors must be taken into account when measuring TEWL and will be discussed in full in an upcoming chapter. In addition, experimental methods and instrumentation used may also affect the outcome of measurements, but can be accurately controlled by using well defined methods and calibrated instruments (Klaus *et al*., 1991; Chilcott *et al*., 2002; Du Plessis *et al*., 2013).

2.5.2.4 Stratum corneum hydration

Skin hydration plays a crucial role in the permeation process, especially for water soluble chemicals (Hatzis, 1995). Stratum corneum hydration reflects the moisture level of the skin's surface (Rawlings, 2006). The state of stratum corneum hydration is dependent on the rate at which water reaches the stratum corneum from the underlying tissues, the rate at which water leaves the surface of the skin by means of evaporation and the ability of the stratum corneum to retain water (Pin, 2011).

Proper hydration of the stratum corneum is critical for proper differentiation and desquamation and to maintain soft, healthy and flexible skin (Lieb *et al*., 1988; Fluhr *et al*., 2008). The stratum corneum makes use of mechanisms to retain water for proper hydration. These mechanisms include: 1) binding of the intercellular lamellar lipids and corneocyte lipids to provide a tight barrier to the passing of water through tissues; 2) corneodemosome-bound interdigitating corneocytes that affect the diffusion path length of water through the stratum corneum; 3) the presence of natural moisturising factors (NMF) in the corneocytes that is derived from the breakdown of filaggrin and consequently trapping the water within the corneocyte cytosol; and 4) endogenous glycerol, that is derived from the sebaceous gland, as a barrier stabilising and moisturising component (Pin, 2011).

Optimal stratum corneum hydration levels range between 20 and 30% in the lower regions of the stratum corneum and decrease to between 5 and 10% at the skin surface. Overhydration of the stratum corneum ultimately leads to disruption of corneocytes and lipids (Stone *et al*., 1998). Corneocytes in the upper layers of the epidermis contain lipids and proteins that bind with water, whereas the protein, filaggrin, is responsible for the secure binding of water in the deeper layers of the epidermis (Bernengo and de Rigal, 2004).

Environmental factors such as relative humidity, temperature and the season also play vital roles in stratum corneum hydration and will influence the outcome of measurements if not kept at optimal levels. Exogenous factors such as wet work, skin washing, occlusion and smoking also influence skin hydration and must be accounted for when interpreting the results. Endogenous factors may also play a vital role and include age, ethnicity, anatomical area, skin temperature and sweat gland activity. In addition to the above factors, experimental methods and instrumentation used may also affect the outcome of measurements, but can be accurately controlled by using well defined methods and calibrated instruments (Hatzis, 1995; Du Plessis *et al*., 2013).

2.5.2.5 Skin surface pH

The pH of the skin can be defined as the negative logarithm of the free hydrogen ion concentration in an aqueous solution (Agache, 2004). The skin surface has an acidic pH ranging from 4 to 7 depending on the anatomical area (Lambers *et al*., 2006). An optimal skin surface pH is necessary to maintain a healthy skin barrier function, stratum corneum integrity, antimicrobial function and skin renewal (Feingold, 2007; Gunathilake *et al*., 2009). An elevation in skin surface pH can lead to many abnormalities in the structure of the extracellular lipid membranes and is directly proportional to a decrease in skin barrier function (Blaak *et al*., 2011). Similarly, many cutaneous inflammatory disorders are also a result of an increased stratum corneum pH, which adversely affects enzyme activity in the stratum corneum. This also decreases the skin barrier function and stratum corneum integrity and cohesion (Feingold, 2007). Skin surface pH is also subject to variability based on several endogenous, exogenous and environmental factors. In addition, experimental methods and instrumentation used may also affect the outcome of measurements,

but can be accurately controlled by using well defined methods and calibrated instruments. Endogenous factors affecting pH measurements include anatomical area, skin condition, age, ethnicity, sebum, skin moisture and sweat. Exogenous factors such as soaps, cosmetics, topical creams and skin irritants also have the ability to influence the pH of an individual's skin surface (Du Plessis *et al*., 2013).

2.5.2.6 Factors affecting skin barrier function

Several endogenous and exogenous factors as well as environmental factors can cause variations in the skin and its barrier function (Du Plessis *et al*., 2013). These factors will be discussed in the following section.

I. Endogenous factors

a) Age

The skin's moisture level of adults will reach a maximum between the ages of 20 and 40, and as the years progress it will become lower because of the decreasing storage capacity of the stratum corneum. TEWL however is age independent for persons in their working years but may decrease in persons older than 60 years (Farinelli and Berardesca, 2006).

b) Gender and Race

Previous literature studies reported contradictory results with regard to the effect of gender on stratum corneum hydration and skin surface pH (Man *et al*., 2009; Du Plessis *et al*., 2013). Previous studies however indicated that darker pigmented skin produced a more resistant skin barrier and also recovered more rapidly after perturbation than those individuals that had lighter skin pigmentation. These findings have remarkable implications for the application of topical or systemic therapeutic agents in terms of transdermal delivery, ability of different skin types to withstand occupational stressors and the effect of hyperpigmentation on the permeability of the skin (Jeffrey *et al*., 1995).

c) Anatomical area

The thickness of the skin varies considerably depending on the anatomical area. The thickest area is the palm of the hand and the soles of the feet, whereas the scrotum

is considered the thinnest (Farinelli and Berardesca, 2006). The thickness of the anatomical areas primarily affects the stratum corneum hydration. The thicker the anatomical area, the higher the stratum corneum hydration, and vice versa (Baryl and Clarys, 2006).

TEWL and skin surface pH are also affected and can be attributed to the regional differences in the lipid content of the stratum corneum. Among anatomical areas, TEWL values tend to be the highest on the palm of hand (Farinelli and Berardesca, 2006).

d) Perspiration

Previous studies concluded that perspiration causes a higher skin surface pH and also causes hypohydration of the stratum corneum due to excessive water loss. Sweating was also associated with higher lipid content, mainly due to increased sweat production (Luebberding *et al*., 2013) Sweating thus also increases TEWL but can be adequately controlled by applying acclimatisation principles to each subject and performing the measurements in a controlled environment under specific ambient temperatures and humidity (Du Plessis *et al*., 2013).

e) Temperature of the skin

The thermoregulatory control of the human body to control blood flow is vital to maintain optimal body temperature. When the body temperature increases during strenuous work, it causes major vasodilatation of the blood vessels, allowing blood flow of up to 6-8 ℓ/min in extreme cases (Charkoudian, 2003). Continuous blood flow is further known to remove xenobiotics from the site where absorption takes place. This in turn causes a concentration gradient which enhances continuous absorption of chemicals. It can thus be proven that an increase in blood flow is associated with an increase in the rate of absorption of chemicals (Luttrell *et al*., 2008; Hayes, 2010).

II. Exogenous factors

a) Personal hygiene practices

The frequency of hand washing and the use of different soaps will have an effect on the stratum corneum integrity. Alkaline soaps are associated with elevated skin surface pH levels, whereas acidic soaps are known to cause only a slight increase or

decrease of the skin surface pH. It has also been proven that skin washing increases TEWL, but will not affect the skin hydration values significantly (Kezic and Nielson, 2009).

b) Use of topical products

Topical products such as barrier creams are widely used in the industry in an attempt to protect intact skin or prevent further damage to skin. The use of these creams have however been associated with lower TEWL readings (Kezic and Nielson, 2009).

c) Occlusion

Although the use of occlusion is common in the enhancement of applied drug penetration, it has substantial effects on the skin barrier function. Skin occlusion is proven to increase stratum corneum hydration with up to 50% (Hafeez and Maibach, 2013). Occlusion as a result of irritation or the wearing of gloves is also known to increase TEWL. Limited information is available on the short term effect of occlusion on skin surface pH, as in the case of workers wearing gloves, but long term effects cause an increase in skin surface pH (Kezic and Nielson, 2009).

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III. Environmental factors

a) Ambient temperature and humidity

The higher the air humidity and room temperature, the higher the moisture content of the skin. Ideal measuring conditions are approximately 20 – 22ºC and 40 – 60% relative air humidity.

2.5.3 Ingestion

Although cobalt is an essential part of our daily diet, excessive exposure through this route can be directly related to personal hygiene habits/conditions in the workplace. Workers who work in cobalt contaminated areas can increase their intake of cobalt if they do not wash their hands prior to smoking or having lunch. Another influential factor is the availability and use of tearooms and designated smoking areas that are separated from the workplace from where the exposure originates (CCOHS, 2009).

Although adequate studies regarding the oral toxicity of cobalt and cobalt compounds in humans are still inconclusive, the most sensitive endpoint following oral exposure appears to be an increase in erythrocyte numbers (ATSDR, 2004).

2.6 Health effects

Toxicity of cobalt is contingent upon duration of exposure, concentration and exposure routes (dermal and respiratory) (Scharf *et al*., 2014).

2.6.1 Respiratory effects

Acute exposure to high levels of cobalt by inhalation results in respiratory effects such as oedema, decrease in respiratory function and haemorrhage of the lung and can be associated with symptoms such as wheezing, coughing and shortness of breath (ATSDR, 2004).

The primary health effects of chronic (long term) exposure to cobalt on respiratory tissues that are associated with hard metal disease include irritation of the respiratory tract, bronchial asthma, fibrotic alveolitis and occasionally diffusive interstitial pulmonary fibrosis (De Palma *et al*., 2010; Permenter *et al*., 2013). The immunological sensitisation to cobalt seems to be responsible for asthma, whereas oxidative stress in the areas of combined lung deposition of cobalt and tungsten is associated with the development of interstitial fibrosis (De Palma *et al*., 2010). Previous studies indicated that exposure to mixtures of cobalt dusts is needed to produce pulmonary fibrosis (Swennen *et al*., 1993; Permenter *et al*., 2013). Bronchial asthma can be associated with symptoms such as wheezing, coughing, dyspnoea and chest tightness in workers exposed to only cobalt dust or other cobalt-containing compounds. An allergic reaction has been postulated in the presence of cobalt-specific IgE antibodies that produce complexes with albumin (Shirakawa *et al*., 1988). These asthmatic symptoms only appear 4-6 hours after exposure to cobalt, and can worsen during the early hours of the night (Barceloux, 1999).

2.6.2 Carcinogenicity

Cobalt is an industrially important metal that bears with it the risk of occupational lung cancer following long term exposure (Angerer, 2006). The International Agency

for Research on Cancer (IARC) has classified cobalt sulphate and other soluble cobalt (II) salts as possible (Group 2B) human carcinogens (IARC, 2006). In most epidemiological studies, the routes of exposure as well as the duration of exposure were of great relevance to determine the risk of tumour development in humans. In the same evaluation, cobalt (II) compounds were reported to induce DNA damage, DNA protein cross links, gene mutations, sister chromatid exchanges and aneuploidy. Additional data indicate that different cobalt species have different influences on toxicity, mutagenicity and carcinogenicity (Lison *et al*., 2001). Although the mechanisms by which cobalt induces cancerous and toxic effects is not well understood, cobalt can mediate free radical generation that may be associated with its carcinogenicity and toxicity (Valko *et al*., 2005). The IARC also reported an increased risk for developing lung cancer that can be associated with high mortality rates after long-term exposure to cobalt, taking into account other factors such as smoking and other occupational carcinogens (IARC, 2006).

2.6.3 Neurotoxic effects

Cobalt neurotoxicity has been reported in isolated cases (Catalani *et al*., 2012). Neurological manifestations that have been confirmed in previous studies include optic nerve damage, decreased visual acuity, tinnitus, bilateral nerve deafness, polyneuropathy, cognitive impairment, memory loss and tremors (Pelclova *et al*., 2012).

2.6.4 Cardiovascular effects

Single cardiomyopathy cases have been linked to workers being exposed to high levels of airborne cobalt in occupational settings. Altered ventricular diastolic function and myocardial stiffness are positively linked to accumulation of cobalt in the myocardium (Scharf *et al.,* 2014; Linna *et al*., 2015).

2.6.5 Haematological effects

Excessive oral exposure to cobalt and cobalt compounds has been demonstrated to increase levels of erythrocytes (polycythemia) and haemoglobin in both humans and animals, but the mechanisms behind this have not been fully elucidated (ATSDR, 2004).

2.6.6 Skin effects

Allergic contact dermatitis is characterised by papules, patches and plaques that lead to vesicle formation and scaling over time. Contact allergens can be defined as small reactive molecules that contain allergic properties. These allergens penetrate the upper layer (stratum corneum) of the skin and cause a cascade of immune reactions due to the interaction of the allergic chemical with the proteins in the skin layers. This interaction causes the formation of hapten-carrier protein complexes that manifests into the sensitisation of the susceptible individual. Allergic contact dermatitis occurs when a previously sensitised individual re-encounters the same hapten, resulting in the manifestation of an elicitation phase, presenting signs such as heat, itching and oedema. Other symptoms include generalized rash, headache, malaise, arthralgia, diarrhoea, vomiting, and fever in severe cases (Sallusto *et al*., 2000; Saint-Mezard *et al*., 2004).

Cross reactions with nickel can also occur (Shirakawa *et al*., 1990), causing complications in the diagnosis of cobalt sensitivity among individuals (Eedy *et al*., 1991). Previous studies also indicated that 1-3% of the general population is allergic to cobalt, with a higher prevalence among woman. A high prevalence of cobalt allergies among women have traditionally been explained by consumer exposure, as it used to be mixed with or occur as an impurity in nickel jewellery (Thyssen and Menné, 2010).

2.7 Biological elimination and monitoring of cobalt

Biological monitoring of chemical exposures in the workplace is becoming increasingly important in the assessment of health risk and as part of the overall occupational health and safety strategy to prevent occupational diseases particularly in the case of multi-route exposure (WHO, 1996). Although additional requirements are needed for this type of monitoring it has several advantages for the worker as well as the company (Morgan, 1997). It is especially useful when there is likely significant absorption through the skin and gastrointestinal system or when the control of the workers' exposure depends on personal protective equipment and it needs to be determined whether their exposure is properly controlled. It is also

essential where there is a reasonably well defined relationship between biological monitoring and effect or where it provides information on accumulated dose and target organ body burden which can be related to toxicity (ACGIH, 2013).

Cobalt can be absorbed mainly through pulmonary routes via inhalation and to a lesser extent through oral ingestion and skin absorption. Not much information is however available on the exact contribution of skin absorption to total body burden. Cobalt is not a cumulative toxin, so regardless of the type of exposure it is mainly excreted in urine and to a lesser extent in faeces (Lauwerys and Lison, 1994). This is why urine has been classified as the best biological matrix to determine the total absorption of cobalt. Urinary levels of cobalt decrease rapidly within 24 hours after the last exposure. The elimination of cobalt in urine can thus be explained by a rapid phase that lasts for a few days. A second slower phase can last up to two years or more (Lison *et al*., 1994). This is where macrophage mediated clearance of the lungs occurs. The rapid phase contributes to 80-90% of the elimination of the absorbed dose. Urinary measurements can thus be used to reflect recent exposure although substantial occupational exposures have been associated with elevated urinary levels for many weeks (Barceloux, 1999; WHO, 2005; CDC, 2012; Hassen and Shanmugan, 2012).

In occupational settings where workers are exposed to cobalt in the air, it is important to distinguish between soluble and insoluble cobalt compounds (Christensen and Poulsen, 1993; Lison *et al*., 1994). Soluble cobalt salts are absorbed better and will evidently produce higher urinary levels in exposed subjects (Linnainmaa and Kiilunen, 1997; Krause *et al*., 2001).

The American Conference of Governmental Industrial Hygienists (ACGIH) made it their mission to use the best available data to set recommended limits to minimize the health risks to workers while at the same time maximising the benefit to society (Morgan, 1997). Following extensive research, the ACGIH stated that the biological exposure index (BEI) for inorganic forms of cobalt (except insoluble cobalt oxides) is 15 µg/ℓ (ACGIH, 2013; Aurelie *et al*., 2014). The BEI is closely linked to the corresponding threshold limit value (TLV) and consequently based on preventing the same health effects addressed by the TLV (Morgan, 1997). Information about the BEI ultimately provides a comparison/reference, and do not necessarily imply that

the BEI is a safe level for general population exposure. The BEI merely indicates a reasonable safe level of exposure below which significant illness, injury or discomfort is unlikely. It is thus not advisable to classify a chemical as hazardous or non-hazardous based on a BEI. This makes it important to always consider biological monitoring complimentary to workplace air monitoring for verifying purposes and to control high risk exposures in the workplace (Morgan, 1997; ACGIH, 2013). Finding a measurable amount of cobalt in the urine does not necessarily mean that it will cause adverse health effects. This only provides reference values to determine whether workers have been exposed to higher levels of cobalt than in the general population (CDC, 2012).

It is of great importance to also take into account that workers' biological exposure to cobalt can also be influenced by several factors including the level of personal hygiene, gender, age, smoking habits, alcohol and nicotine consumption and dietary habits and will be visible in the urine cobalt content (Linnainmaa and Kiilunen, 1997). The progressive improvement of personal and hygienic conditions in the workplace is becoming more important due to its extra-occupational influence on the levels of biomarkers (Lorenzo *et al*., 1995). Factors like frequency of hand washing, eating and smoking with contaminated hands and also eating and smoking in contaminated areas have been proven to interfere with the metabolism of substances absorbed in the workplace. Alcohol, drugs and tobacco have the potential to modify biological exposures in exposed subjects. Excessive alcohol consumption has the ability to inhibit the individuals' metabolism, whereas regular alcohol consumption is associated with induction of the metabolism. Urine levels will also vary depending on the type of cobalt compound exposure. Occupational exposure to soluble cobalt salts will produce proportionally higher urinary levels because they are absorbed faster than other cobalt compounds (Kraus *et al*., 2001; Linnainmaa and Kiilunen, 1997).

It can thus be concluded that many routes of exposure may contribute to the total absorption of cobalt in the body. This study will thus ultimately focus on these individual routes of exposure as well as the total effect it has on the urine cobalt content of exposed subjects.

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This article exceeds the limit of 5000 words (excluding the abstract and references) because it was completed for exam purposes and is therefore done very thoroughly.

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CHAPTER 3: ARTICLE

ASSESSMENT OF THE OCCUPATIONAL EXPOSURE TO COBALT AT A BASE METAL REFINERY

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ABSTRACT

Objectives: The objectives for this study were (i) to assess the respiratory exposure of base metal refinery workers to cobalt sulphate; (ii) to assess the dermal exposure of these workers to cobalt sulphate; (iii) to assess the skin barrier function by means of TEWL, skin hydration and skin surface pH; (iv) to assess workers' urine cobalt concentration by means of biological monitoring and; (v) to determine the contribution of each exposure route to the total urine content.

Methods: The study was conducted at a base metal refinery where workers stationed in a Cobalt plant (20 workers) and Packaging plant (5 workers) are potentially exposed to soluble cobalt sulphate through respiratory and dermal exposure routes. Evaluation of the respiratory exposure was quantified using the Institute of Occupational Medicine (IOM) aerosol sampler. Evaluation of the dermal exposure included quantification of the cobalt deposition on the skin using Ghostwipes™ as a removal method, while TEWL, skin hydration and pH measurements were used to determine the change in skin barrier function. Dermal measurements were done on four different anatomical areas (forearm, wrist, palm of hand and back of hand) before, during and after the working shift. Evaluation of the cobalt content in the urine of employees was included to evaluate the exposure through all exposure routes (respiratory and dermal).

Results and Discussion: Occupational exposure to cobalt at a base metal refinery was detected through the respiratory and dermal routes of exposure. High inhalable airborne exposures above the Occupational Exposure Limit - Time Weighted Average (OEL-TWA) were noted for several workers in both the Cobalt and Packaging plant of the base metal refinery. Respirable fractions only contributed a small fraction of the total airborne exposure to cobalt. Detectable levels of cobalt were found on the skin of exposed workers in both the Cobalt and Packaging plant with geometric means ranging between 0.104 µg/cm^2 on the back of hand and 77.600 µg/cm^2 on the wrist. The majority of measurements indicated an increase in TEWL percentage changes from the beginning to the end of the shift, with a decrease being reported in all skin hydration measurements, and pH indicating high variability between the Cobalt and Packaging plant. Biological monitoring data

indicated baseline urine levels above the Biological Exposure Index (BEI) of 15 µg Co/g Creatinine in five out of the 12 workers in the Cobalt plant. The mean urine cobalt concentration in Cobalt plant workers decreased slightly from a baseline measurement of 17.83 µg Co/g Creatinine to 12.37 µg Co/g Creatinine on day 5. Workers' urine levels in the Packaging plant however indicated cobalt concentrations of approximately three times lower than the recommended BEI, with levels ranging between a baseline measurement of 2.5 µg Co/g Creatinine and 6.6 µg Co/g Creatinine on day 5. Pair wise correlations indicated significant strong positive correlations between dermal exposure and biological monitoring (change in urine cobalt concentration between Day 3 and the Baseline) in the Cobalt plant and the Cobalt and Packaging plants combined.

Conclusion: Refinery workers are exposed to cobalt sulphate (liquid solution and cobalt sulphate crystals) through the respiratory and dermal routes of exposure in both the Cobalt and Packaging plant of the base metal refinery, of which only dermal exposure significantly correlated with the total urine content of the workers. Changes in the skin barrier function also indicated that the skin integrity was compromised.

Keywords: respiratory exposure, dermal exposure, barrier function, transepidermal water loss, skin hydration, skin surface pH, biological monitoring, cobalt sulphate, refinery, occupational health risk

INTRODUCTION

South Africa has a thriving mining industry and is known as one of the largest producers of platinum group metals (PGMs) (Wiseman and Fathi, 2009). In occupational settings such as refineries, cobalt sulphate is mainly produced as a by-product of PGMs and nickel and copper refining. These settings are seen as the main contributors in terms of exposing workers to potentially unhealthy working environments. Metals such as cobalt can thus be seen to play a vitally important role in the health status of exposed workers (Lison *et al*., 1994; Cherrie *et al*., 2006).

Cobalt can be described as a natural earth element that is known for its high value and multiple uses in industrial and agricultural settings (IARC, 2006). It is also an essential oligo-element that plays a vital role in the formation of vitamin $B_{12.}$ This vitamin contains approximately 4% cobalt and is needed for normal functioning of the nervous system, in particular the brain, and the formation of blood (Lauwerys and Lison, 1994).

Occupational exposure to excessive levels of cobalt can however cause adverse health effects through inhalation, skin contact and to a lesser extent ingestion (Lauwerys and Lison, 1994). A previous study conducted at a base metal refinery indicated respiratory and dermal exposure in a packaging plant (Eloff *et al*., 2011). Much research has also been directed towards exploring the interrelated mechanisms associated with the different routes of exposure, but proper understanding of these processes is still incomplete and open for further exploration.

Multiple adverse health effects related to excessive cobalt exposure have been documented. These health effects relate back to specific target organs such as the lungs, skin, thyroid gland, myocardium and bone marrow (Swennen *et al*., 1993; ATSDR, 2004). Cobalt and its compounds are classified as a possible (Group 2B) human carcinogen by the IARC, with well documented animal experimental studies supporting a risk for developing lung cancer with high mortality rates following long-term exposure to cobalt (Lasfargues *et al*., 1992; Tüchsen *et al*., 1996; Moulin *et al*., 1998; IARC, 2006). Other related respiratory effects of cobalt inhalation include effects such as oedema, decrease in respiratory function and haemorrhage of the lung, which results in symptoms such as wheezing, coughing and shortness of breath (ATSDR, 2004).

Skin related disorders discerning from cobalt exposure include sensitisation that lead to allergic contact dermatitis (ACD) in sensitive subjects (Shirakawa *et al*., 1990; Filon *et al*., 2004; Julander *et al*., 2010). The condition of the skin plays a vital role in the susceptibility of individuals to local and sensitised skin toxicity (Kezic and Nielsen, 2009). Skin hydration, surface pH and transepidermal water loss are key factors that indicate the integrity of the skin barrier. These measurements are thus of vital importance when determining the skin barrier function of exposed subjects (Verdier-Sévrain and Bonté, 2007). This is supported by previous *in vitro* studies which found that cobalt powders permeated through damaged/compromised skin to a greater extent than through healthy intact skin (Larese Filon *et al*., 2009).

Skin disorders such as ACD can be an enormous burden for both the employer and the worker (Stefaniak *et al*., 2012). This is especially true due to the high costs involved with medical health care and compensation to the workers suffering from these disorders. Sensitised workers on the other hand, face lifelong avoidance of repeat exposure to prevent elicitation of an allergic reaction. This puts enormous physical and emotional strain on the worker in terms of discomfort as well as fear of loss of income due to inability to work in contaminated areas (Holness and Nethercott, 1995).

Multiple exposure routes ultimately lead to higher exposure. In order to account for all routes of exposure, biological monitoring is of vital importance. Biological monitoring is becoming increasingly important in the assessment of health risks, especially when there is likely absorption through multiple routes of exposure (WHO, 1996). Cobalt is not a cumulative toxicant and is mainly excreted in the urine in two phases. The first phase contributes to approximately 80-90% of the elimination of cobalt in just a few days following the last exposure. The remaining dose is ultimately eliminated over a period of two years or more (Lison *et al*., 1994). This makes urine the best biological indicator for determining total cobalt absorption following recent exposure (Lauwerys and Lison, 1994).

This study was conducted at a base metal refinery where workers are stationed in two cobalt production areas and potentially exposed to cobalt via multiple routes of exposure. The main objectives were to assess the respiratory and dermal exposure of refinery workers to cobalt sulphate and to determine the skin barrier function, as

well as to assess the workers' urine cobalt concentration by means of biological monitoring. In addition, the respiratory and dermal exposures were correlated with the biological exposure to establish the contribution of each route of exposure to the total exposure.

METHODOLOGY

Design and workplace description

The study was conducted at a base metal refinery where workers are potentially exposed to soluble cobalt sulphate through respiratory and dermal exposure routes.

The base metal refinery receives concentrated matte from a smelter and converting plant where the PGMs get separated from the base metals. The PGMs are sent to a precious metal refinery (PMR) for further refining into precious metals, while the base metals undergo a process of leaching and purification whereby cobalt is recovered in the form of $CoSO_4 \cdot 7H_2O$ in a cobalt plant and packed in a packaging plant.

Two production areas, namely the Cobalt plant and Cobalt Packaging plant, within the base metal refinery were thus identified as a possible concern for cobalt exposure.

The Cobalt plant is operated by 20 workers over four working shifts. Only 12 out of the 20 employees participated in the study and included eight workers occupied in the Solvex and Purification section, and the rest operating the Crystalliser. The Cobalt plant can thus be divided into three stages:

1. Purification section – Cobalt and nickel slurry cake are dissolved in sulphuric acid and formaldehyde to precipitate iron and copper impurities. Pure cobalt and nickel filtrate (liquid state) are sent for solvent extraction.

2. Solvent extraction (Solvex) – Contains 19 cells that selectively extract cobalt from the feed solution to acceptable concentrations, thus separating nickel and cobalt. Pure cobalt stream (liquid state) is then sent for crystallisation.

3. Crystalliser section – The cobalt stream is pre-heated in a heat exchanger and then evaporated under vacuum in a double effect crystalliser to produce stable cobalt sulphate crystals. The cobalt sulphate is then sent to the packaging plant for bagging and despatch.

The Packaging plant is separate from the Cobalt plant and receives cobalt sulphate crystals in bulk bags that are hoisted up and released into a funnel. The cobalt crystals are then accurately packed into 25 kg bags, sealed and shipped in large one ton containers.

The Packaging plant can also be divided into two sections:

1. Unscreened area – product received from the Cobalt plant is placed in a hopper and bagged. This section bags the cobalt sulphate crystals as well as finer cobalt sulphate particles as received from the Cobalt plant.

2. Screened area – product received from the Cobalt plant is further processed into finer particles by means of a sifting process that separates the crystals from the finer dust. This section only bags the finer cobalt sulphate particles.

Four to five workers are stationed at different substations within the Cobalt Packaging plant. Three workers were selected to take part in the study over a period of four days while bagging operations took place.

Method for the assessment of respiratory exposure

The study included the quantification of the respirable and inhalable fraction of exposure. Respiratory exposure sampling is part of a legal compliance occupational hygiene monitoring programme being conducted at the base metal refinery. Informed consent was also obtained from the workers to partake in the measurements. Personal airborne dust sampling was carried out by using the Institute of Occupational Medicine (IOM) inhalable aerosol sampler, as well as 0.8 µm cellulose ester membrane filters and cellulose back-up pads. To measure the respirable fraction, the same IOM-sampler was used, but a cellulose foam filter pad was inserted to represent respirable exposure. A Gilian (Gilair-3, Sensidyne) air sampling pump was used for sampling the airborne concentrations in the workplace. The fully

charged sampling pump was calibrated at a constant flow rate of 2.0 ℓ/min. Personal sampling was conducted by attaching the IOM-sampler within the worker's breathing zone (clips). Average sampling time in the Cobalt plant was 5-6 hours of the 8-hour shift due to shift changes and morning safety talks. Sampling time in the Packaging plant varied between 2 and 6 hours as this bagging operation is not operated continuously. After sampling commenced, the sampling pump flow rate was verified to ensure it did not differ by more than 5% of the pre flow rate. Sample analysis was performed by an accredited laboratory using OHSA ID-121, with a detection limit of 0.0002 mg/sample (OSHA, 2002).

Method for the assessment of dermal exposure

The removal method used in this study consisted of wiping the skin contaminant layer with a commercially available skin wipe known as Ghostwipe™. Each wipe had been individually wrapped by the supplier and consisted of a 15 cm × 15 cm non-woven fabric sheet that was pre-moistened with de-ionized water, providing a greater consistency for the moisture content. Disposable transparent templates with a rectangular area of 25 cm^2 were also used to maintain a standard surface sampling area. A clean template was used for each sample by holding the template on the desired sampling area with one hand and using the other hand to wipe the exposed skin area with the Ghostwipe™. The skin of workers was wiped before washing their hands and faces in order to ensure an accurate representation of the level of skin contamination during the shift. Each sample consisted of a single wipe that was used to wipe the area four consecutive times, folding it in half after each wipe in an overlapping s-pattern. Clean vinyl/nitrate gloves were used for every wipe sample taken. Four anatomical areas were assessed to evaluate skin exposure to cobalt. These areas were the palm, back of hand and wrist of the dominant hand and the forearm. A wet wipe was used to wipe all the representative anatomical areas clean before commencement of their shift in order to eliminate any external contamination that the workers were exposed to outside their working environment. Sampling was conducted on morning shift workers during their shift (prior to lunch or break) and at the end of shift. Total cobalt deposition on the skin was also used to enable establishment of correlations with both the biological monitoring data, as well as the respiratory data. Sample analysis was performed by an accredited laboratory using OHSA Method ID-121 with a detection limit of 0.0002 mg/sample (OSHA, 2002).

Method for the assessment of the skin barrier function

To determine the skin barrier function, it was necessary to measure the level of hydration and TEWL using a Corneometer (Courage and Khazaka, Germany) and Vapometer (Delfin Technologies Ltd, Finland), respectively. The Corneometer measures the capacitance contribution of the skin in contact with the measuring probe (Barel and Clarys, 2006), where low readings indicate dry skin and vice versa. The Vapometer is an unventilated closed chamber instrument that measures TEWL. The pH of the skin surface was measured with a Derma Unit SSC3 (Courage and Khazaka, Germany). Two measurements for TEWL and three measurements for skin hydration and skin surface pH were made on the palm, back of hand, wrist and forearm. The hydration, TEWL and pH measurements were conducted on the same workers where they were acclimatized for 10 minutes in an air conditioned tea room before commencement of the measurements. The conditions in the tea room were controlled and recorded to eliminate any direct sunlight and to provide optimal humidity (40-60%) and temperature (20-22˚C) conditions.

All exposure data were presented as percentage changes using the following formula (where X represents the reading taken from the measuring device used):

$$\text{Percentage change over shift} = (X_{\text{End of shift}} - X_{\text{Beginning of shift}} / X_{\text{Beginning of shift}}) \times 100$$

This was done to account for the lack of consensus with regard to reference values for the different parameters, making the use of absolute values problematic (Du Plessis *et al.,* 2013).

Biological monitoring

In addition to respiratory and dermal measurements, biological monitoring was included in this study to provide information on the absorption, metabolism and elimination of cobalt in the body. Biological monitoring is also part of a legal compliance occupational hygiene monitoring programme being conducted at the base metal refinery under the guidance of an Occupational Medical Practitioner (OMP). From an ethical point of view, informed consent was also obtained from the workers to partake in the study after providing them with the necessary objectives for the biological monitoring, such as what samples were to be taken, for what purpose and what would be done with the data. All data were treated as confidential but were

open to the involved worker, who also had the right to medical opinions. An important aspect that was communicated to each worker is the importance of a 72 hour seafood free diet prior to the testing (WHO, 2006).

The half-life of cobalt in the body ranges from approximately 5 days to a couple of years. In order to assess the workers' recent exposure to cobalt, samples were taken before the shift at the beginning of the work week (baseline), 3 days after first exposure at the end of the shift and at the end of the shift at the end of the 5 day work week (Lison *et al*., 1994; ACGIH, 2013). Polyethylene containers were used that were soaked overnight in 10% nitric acid to avoid contamination from the container. Urine samples were stored and transported with adequate insulation and stored on dry ice with no preservatives. These precautions ensured that conjugates were not hydrolysed, micro-organism growth prevented and that volatile constituents were not lost. A creatinine correction factor was also determined to account for worker fluid intake and urine dilution. Urinary cobalt concentrations were determined by the Graphite Furnace Atomic Absorption Spectrometry (GFAAS) method by an accredited laboratory (EPA, 2007).

Observations and Personal Protective Equipment (PPE)

Non-routine tasks were noted during the sampling period and were accounted for where applicable.

Standard and special PPE requirements were evident when working in both sections. PPE was taken off randomly during the shift, especially the gloves during breaks. Cobalt plant employees were protected with a two-piece green acid resistant overall, Bova™ safety shoes, rubber gloves, hard hat, safety glasses, hearing protection, and 3M™ FFP2 respiratory protection. Respiratory protection was only compulsory in the Crystalliser section when bagging of cobalt sulphate was taking place. Cobalt packaging workers were protected with a two-piece green acid resistant overall with an additional Tyvek™ coverall suit, Bova™ safety shoes, rubber gloves, hard hat, safety glasses, and Drὰger® airstream helmets to provide fresh breathable air while bagging the cobalt sulphate.

Statistical analysis

All data were statistically analysed based on differences in the Cobalt plant and the Cobalt and Packaging plants combined, despite subsections being present in both areas due to the low number of workers present in each area.

Airborne exposure data were analysed using GraphPad Prism 6 (GraphPad Software Inc). The inhalable and respirable airborne exposures were statistically analysed with unpaired t-tests. The p-value was considered as statistically significant at $p \leq 0.05$.

Cobalt collected from the skin and skin parameters (percentage change in TEWL, skin hydration and pH) were analysed using Statistica 12 (Statsoft Inc). The skin exposure data were log transformed for analysis as it was not distributed normal. Repeated measures analysis of variance (ANOVA) with effect sizes and powers were used to determine interactions between the dependent variables (anatomical areas and time). Repeated measures ANOVA with Bonferroni post-hoc tests further indicated the specific statistically significant differences between the dependent variables in both the Cobalt plant and the Packaging plant.

Pairwise correlations between respiratory, dermal and biological monitoring data were also determined for the Cobalt plant and Cobalt and Packaging plants combined. The following variables were used to determine the correlations:

- Inhalable TWA exposure vs Biological monitoring (Day 3 – Baseline)
- Inhalable TWA exposure vs Biological monitoring (Day 3)
- Respirable TWA exposure vs Biological monitoring (Day 3 – Baseline)
- Respirable TWA exposure vs Biological monitoring (Day 3)
- Dermal exposure (gm) vs Biological monitoring (Day 3 – Baseline)
- Dermal exposure (geometric mean) vs Biological monitoring (Day 3)
- Inhalable TWA exposure vs Dermal exposure (geometric mean)
- Respirable TWA exposure vs Dermal exposure (geometric mean)

Note: Biological monitoring data for Day 5 was discarded for correlations due to insufficient amount of samples obtained on this day.

Correlations between the respiratory, dermal and biological monitoring data were done using GraphPad Prism 6 (GraphPad Software Inc). Skewness and kurtosis tests for pairwise correlations indicated that non parametric Spearman correlations were appropriate.

RESULTS

A total of 25 employees were stationed in the areas included in this study of which 15 participated in the study.

Respiratory exposure

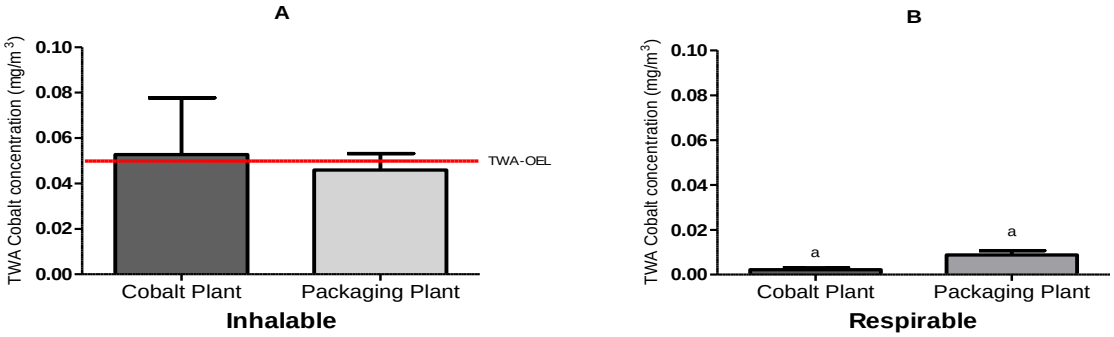

Figure 1: Mean airborne exposures depicting the (A) inhalable fraction (n=15), and (B) respirable fraction (n=15)(mean ± SD). Statistical significant difference as determined by an independent t-test is indicated by a. The inhalable TWA-OEL of Cobalt is indicated (0.05 mg/m^3).

The mean inhalable exposure in the Cobalt plant and Packaging plant was 0.053 mg/m^3 and 0.046 mg/m^3 respectively (Figure 1A). It is evident from the results that on average the Cobalt plant employees had exposures above the TWA-OEL of 0.05 mg/m^3, with the Packaging plant employee exposures being just below the TWA-OEL. No statistically significant differences were detected between the inhalable exposures in the Cobalt and Packaging plant.

The mean respirable exposure in the Cobalt plant and Packaging plant was 0.002 mg/m^3 and 0.009 mg/m^3 respectively (Figure 1B). It is evident that the respirable fraction of exposure was higher in the Packaging plant employees than in the Cobalt plant employees. Independent t-tests between the production areas indicated a statistically significant difference in the respirable airborne exposure data indicated by a ($p = 0.004$).

Dermal exposure

Table 1: Cobalt removed from the skin of workers in the Cobalt plant and Packaging plant. GM indicates total dermal exposure during the shift (i.e. sum of Before Lunch and End of Shift)

Plant area	Anatomical areas	Sampling intervals	µg/cm^2				
			Interval GM	GM	GSD	Min	Max
Cobalt plant (n=12)	Forearm	Before Lunch	0.675	0.784[a]	0.565	0.144	9.432
		End of Shift	0.910				
	Wrist	Before Lunch	1.569	1.420[b]	3.293	0.176	77.600
		End of Shift	1.286				
	Palm of hand	Before Lunch	3.818	3.383[a,b,c]	2.126	0.232	40.416
		End of Shift	2.998				
	Back of hand	Before Lunch	1.739	1.264[c]	1.789	0.120	33.352
		End of Shift	0.918				
Packaging Plant (n=3)	Forearm	Before Lunch	0.530	0.884	2.906	0.360	17.936
		End of Shift	1.474				
	Wrist	Before Lunch	1.279	1.919	9.089	0.200	55.872
		End of Shift	2.879				
	Palm of hand	Before Lunch	1.438	2.073	12.528	0.216	76.416
		End of Shift	2.988				
	Back of hand	Before Lunch	0.746	0.891	2.694	0.104	16.824
		End of Shift	1.064				

a,b,c represent a statistically significant difference between the anatomical areas measured in the Cobalt plant as indicated by repeated measures ANOVA with Bonferonni post hoc tests. GM = Geometric Mean; GSD = Geometric Standard Deviation; Min = Minimum; Max = Maximum.

Detectable levels of cobalt ranging from 0.120 µg/cm^2 to 77.600 µg/cm^2 in the Cobalt plant and 0.104 µg/cm^2 to 76.416 µg/cm^2 in the Packaging plant were removed from the skin of exposed workers (Table 1). In both the Cobalt plant and Packaging plant, full-shift exposures were the highest on the palm of the hand with geometric means of 3.383 µg/cm^2 and 2.073 µg/cm^2, respectively. In both the Cobalt plant and Packaging plant, exposure was the lowest on the forearm with geometric means of 0.784 µg/cm^2 and 0.884 µg/cm^2, respectively.

Repeated measures ANOVA with effect sizes and powers showed interactions between the different anatomical areas (forearm, wrist, palm of hand and back of hand) of workers in the Cobalt and Packaging plant ($p \leq 0.002$). A repeated measures ANOVA with a Bonferroni post-hoc test further indicated that there were statistically significant differences between the cobalt removed from the different anatomical areas of workers in the Cobalt plant. Exposure on the palm of the hand differed significantly with that of the forearm ($p \leq 0.001$), the wrist ($p = 0.005$) and the back of hand ($p = 0.007$) (Table 1).

Skin barrier function

Mean percentage changes in TEWL on the different anatomical areas from the beginning to the end of the shift in both production areas were found to be variable. In both the Cobalt and Packaging plant, the forearm indicated a decrease in TEWL with percentage changes of 52.68% and 26.27%, respectively, while the palm of hand and the back of hand indicated increases in TEWL of between 18.13% and 67.83%. TEWL on the wrist however decreased by 21.51% in the Cobalt plant and increased by 76.22% in the Packaging plant (Figure 2).

Repeated measures ANOVA with effect sizes and powers showed interactions between TEWL on the different anatomical areas (forearm, wrist, palm of hand and back of hand) measured in the Cobalt plant ($p \leq 0.002$), with no significant differences detected in the Packaging plant due to the small sample size. A repeated measures ANOVA with a Bonferroni post-hoc test indicated that there were statistically significant differences in TEWL measured in the Cobalt plant. TEWL on the back of the hand differed significantly from that of the forearm ($p \leq 0.001$), the wrist ($p \leq 0.001$) and the palm of hand ($p \leq 0.001$).

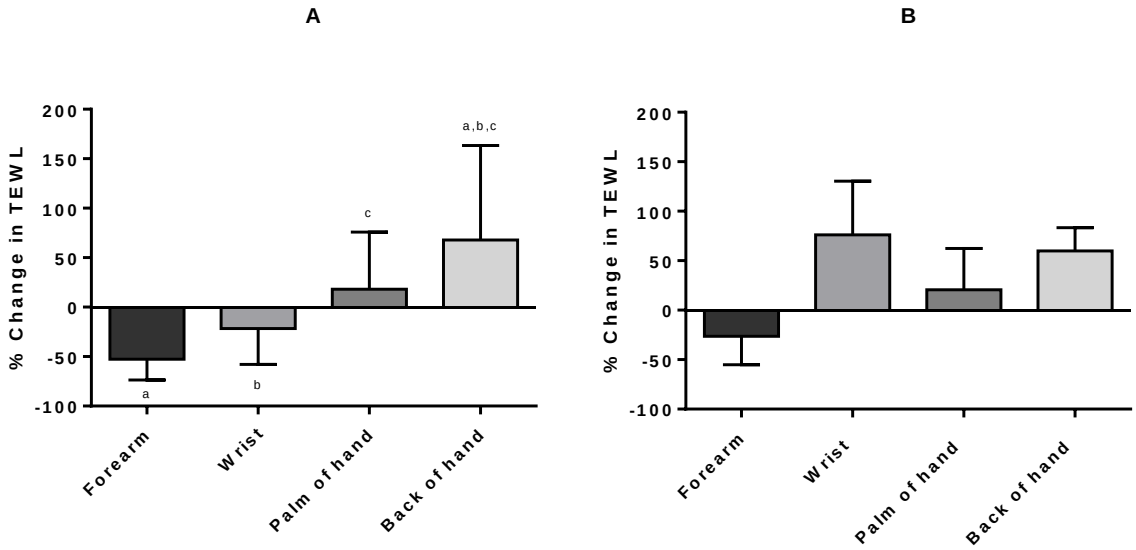

Figure 2: Percentage changes in TEWL (mean ± SD) measured on the different anatomical areas in (A) Cobalt Plant (n=12), (B) Packaging plant (n=3).

Mean percentage changes in skin hydration on all anatomical areas from the beginning to the end of the shift in both production areas indicated a decrease in skin hydration ranging between 10.92% and 39.66% (Figure 3).

Repeated measures ANOVA with effect sizes and powers showed interactions between skin hydration on the different anatomical areas measured in both the Cobalt ($p \leq 0.001$) and Packaging ($p = 0.004$) plant. Repeated measures ANOVA with a Bonferroni post-hoc test indicated that there were statistically significant differences between the skin hydration measured on the different anatomical areas in both production areas. Skin hydration on the forearm differed significantly from that of the wrist ($p = 0.018$) in the Cobalt plant and the forearm differed significantly from the wrist ($p = 0.029$), palm of hand ($p = 0.031$) and the back of hand ($p = 0.007$) in the Packaging plant.

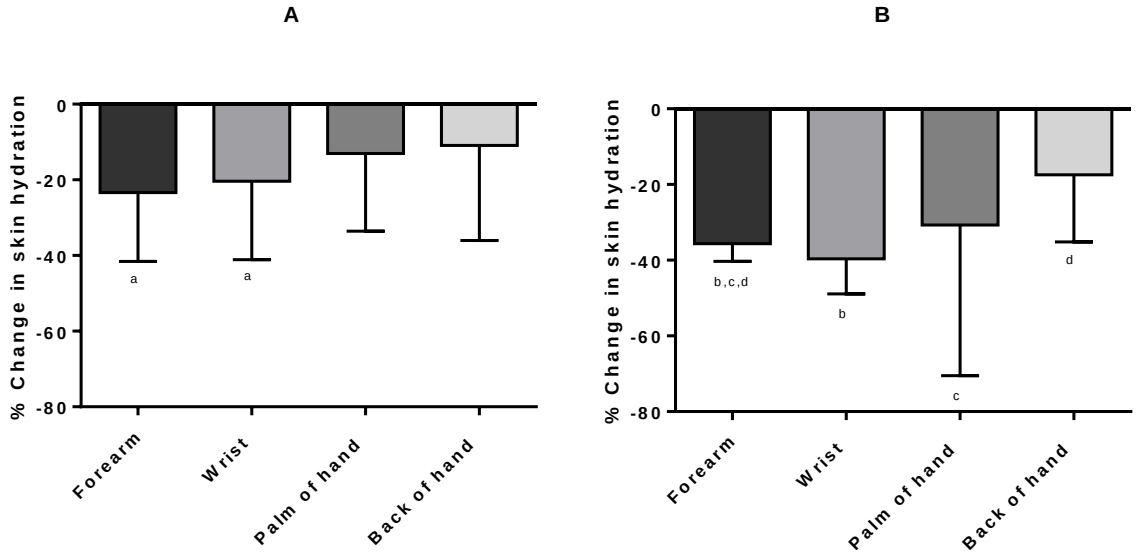

Figure 3: Percentage changes in skin hydration (mean ± SD) measured on the different anatomical areas in (A) Cobalt Plant (n=12), (B) Packaging plant (n=3).

All four anatomical areas of workers in the Cobalt plant indicated an increase in skin surface pH from the beginning to the end of shift. Increases ranged between 2.04% and 27.29%. Three anatomical areas of workers in the Packaging plant indicated a decrease in skin surface pH, with decreases ranging between 2.26% and 7.53%, the exception being the forearm which indicated an increase of 0.84% (Figure 4).

Repeated measures ANOVA with effect sizes and powers indicated significant correlations between the pH measured on the different anatomical areas sampled in the Cobalt plant ($p \leq 0.001$), with no significant differences detected in the Packaging plant due to the small sample size. A repeated measures ANOVA with a Bonferroni post-hoc test indicated that there were statistical significant differences between the pH measured on the different anatomical areas in the Cobalt plant. pH on the palm of the hand differed significantly with that of the forearm ($p = 0.004$), wrist ($p \leq 0.001$) and back of hand ($p = 0.004$).

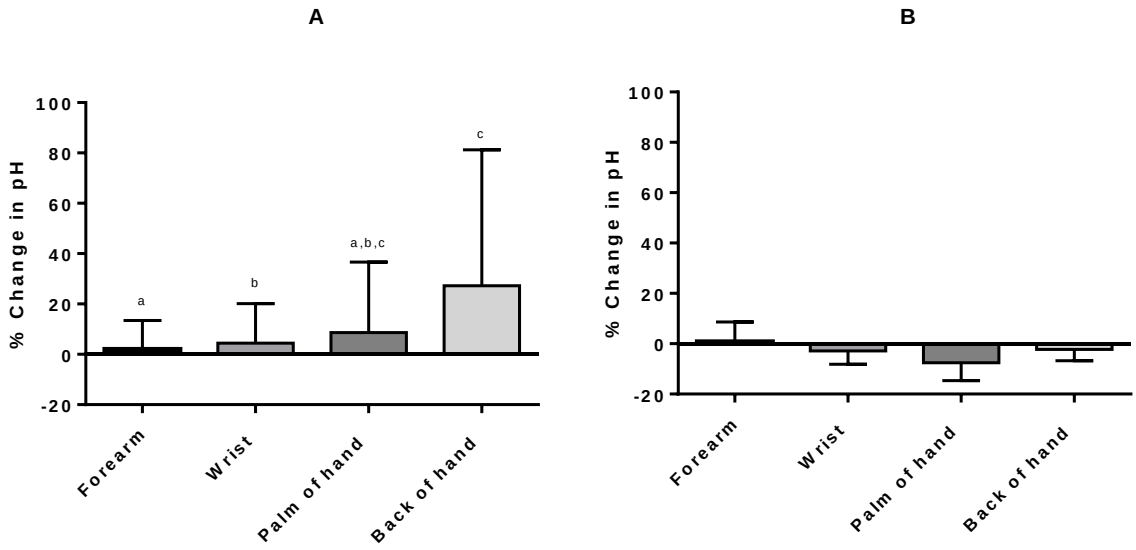

Figure 4: Percentage changes in skin surface pH (mean ± SD) measured on the different anatomical areas in (A) Cobalt Plant (n=12), (B) Packaging plant (n=3).

Biological monitoring

It is evident from the results that the baseline urine cobalt content in the Packaging plant workers was approximately three times lower than the recommended BEI, while that of the Cobalt plant exceeded the BEI. The mean urine cobalt concentration in Cobalt plant workers indicated a non-significant decrease in concentration of urine cobalt from the baseline measurement (17.83 µg Co/g Creatinine) to day 3 (15.65 µg Co/g Creatinine). A further slight decrease, although statistically insignificant, was noted from day 3 to day 5 (12.37 µg Co/g Creatinine). Packaging plant workers showed slight increases, although statistically insignificant due to the small sample size, from the baseline (2.5 µg Co/g Creatinine) to day 3 (4.47 µg Co/g Creatinine) and day 5 (6.6 µg Co/g Creatinine). None of the samples taken from workers in the Packaging plant exceeded the BEI.

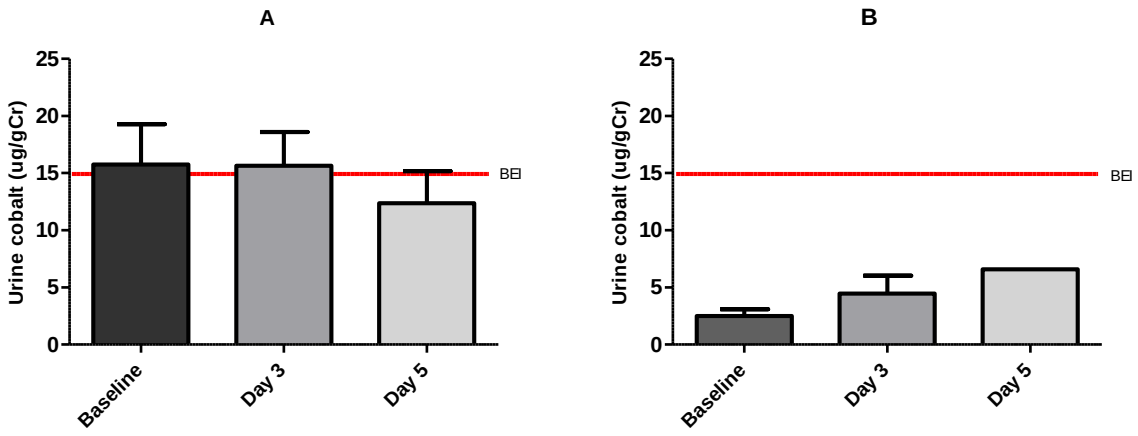

Figure 5: Urine cobalt concentrations (µg/g Creatinine) in A) Cobalt Plant (n=12), B) Packaging plant (n=3) represented by a baseline and samples collected at the end of day 3 and 5. BEI based on the international standard of 15 µg Co/g Creatinine as set by the ACGIH.

Correlations between Respirable exposure, Dermal exposure and Biological Monitoring

Pairwise correlations were done for Cobalt plant and Cobalt and Packaging plant combined to determine if there were any significant correlations between the variables (Tables 1 and 2– Supplementary material).

No significant correlations were found between any of the variable combinations except for dermal exposure versus biological monitoring (Change in urine Cobalt concentration: Day 3 – Baseline) in the Cobalt plant and the Cobalt and Packaging plant combined. Significant strong positive correlations were found ($r = 0.857$; $p = 0.024$) and ($r = 0.867$; $p = 0.005$), respectively.

DISCUSSION

Occupational exposure to cobalt at a base metal refinery has proven to occur through the respiratory and dermal routes of exposure. A previous study only reported on exposure in the packaging plant of a base metal refinery (Eloff *et al*., 2011). Other studies include assessment of dermal exposure (skin barrier) to selected metals in refinery workers (Du Plessis *et al*., 2013). However, to the best of the author's knowledge there are no previous studies to support airborne cobalt exposure in earlier stages of cobalt production as is the case of the cobalt plant of a base metal refinery. Based on the results of this study, one can clearly observe that the majority of airborne exposures in the Cobalt and Packaging plant are to inhalable fractions of cobalt, with respirable exposure contributing only a small fraction of the total exposure. Inhalable exposures indicated results that exceeded the OEL of 0.05 mg/m³ in the Cobalt plant (0.053 mg/m^3 average), with the Packaging plant workers' exposures just below the TWA-OEL with an average exposure of 0.046 mg/m^3. Average respirable concentrations were significantly higher in the Packaging plant (0.009 mg/m^3) than that in the Cobalt plant (0.002 mg/m^3). Based on the process literature it can be expected that inhalable exposures will include a much higher fraction of the total airborne exposure than the respirable fraction in the Cobalt plant, based on the physical form of the cobalt in the two sections, containing both liquid and dust forms. The Packaging plant on the other hand is partly associated with a much finer dispersible form of dust (screened section) resulting in the total airborne exposures containing a slightly larger fraction of respirable dust than in the Cobalt plant.

Cobalt deposition on the skin was assessed by making use of a removal method. Results indicated readily detectable, but highly variable, levels of cobalt on all four anatomical areas measured. Previous studies done on nickel also reported on variable levels of skin deposition (Du Plessis *et al*., 2010; Du Plessis *et al*., 2013). The palm of hand was found to be the most exposed anatomical area in both the Cobalt plant and Packaging plant. This can be supported by previous studies that also identified the palm of hand as one of the most exposed anatomical areas measured (Du Plessis *et al*., 2010; Du Plessis *et al*., 2013). The position of the exposed anatomical area can also indicate that if the gloves fail, it will be in direct contact with the cobalt due to the physical handling/operation of the plant processes.

The forearm was the least exposed in the Cobalt plant, with the forearm and back of hand being the least exposed anatomical areas in the Packaging plant. Contamination can be assumed to be a reason for exposure on the forearm due to contaminated clothing and removing of contaminated gloves during lunch and after the shift. This also correlates with a previous study (Du Plessis *et al*., 2010). Lower levels of cobalt deposition on the back of hand can also be explained by the physical position of the anatomical area that was not in direct contact with cobalt due to the physical handling/operation of the plant processes.

Changes in the workers' skin barrier function were assessed by measurements of TEWL, skin hydration and skin surface pH over time. The palm of the hand and back of hand indicated increases in TEWL, with decreases being recorded for the wrist and forearm in the Cobalt plant from before shift to end of shift. The Packaging plant indicated increases in TEWL for all anatomical areas except the forearm. The majority of the results indicate an increase in TEWL, which according to supported literature, is a sign of skin damage due to exposure to chemicals and physical conditions (Barel and Clarys, 1995). External physical factors such as sweating were controlled as far as reasonably practicable by applying acclimatisation principles during the measuring period in a controlled environment under specific ambient temperatures and humidity. Occlusion due to the wearing of gloves was also identified as a possible influential factor in the case of increased TEWL readings (Du Plessis *et al*., 2013). A study done by Du Plessis *et al.* (2013) in a similar base metal refinery also presented similar results where an increase in TEWL was observed in most workers, on most anatomical areas measured. This is also supported in another study where a significant increase in TEWL was reported in refinery workers (Du Plessis *et al*., 2010).

Stratum corneum hydration primarily indicates the water content of the skin. Results indicated a fairly consistent decrease during the shift on all anatomical areas measured in the Cobalt and Packaging plant. Several factors such as the anatomical area measured must be considered. These findings negatively impact the skin barrier function and are in accordance with consistent decreases in stratum corneum hydration in a similar study done by Du Plessis *et al*. (2013).

The pH of human skin is responsible for regulating the formation of the skin barrier (Feingold, 2007). In the Cobalt plant all four anatomical areas indicated an increase in skin surface pH from the beginning to the end of shift, while three anatomical areas in the Packaging plant indicated a decrease in skin surface pH, the exception being the forearm. One would have expected pH values in the Cobalt plant to decrease due to acidic manipulation where the pH is regulated between 2 (sulphuric acid and formalin) and 4.8 (caustic soda) where the pure cobalt stream is separated from the nickel stream (personal communication).

To conclude the findings, most of the TEWL increased, with a decrease being reported for stratum corneum hydration, and pH measurements increased in the Cobalt plant while a decrease was noted in the Packaging plant. Higher TEWL values are associated with a loss in skin barrier function, while a decrease in stratum corneum hydration indicates dehydrated skin that affects the skin barrier adversely. A decrease in skin surface pH is also associated with increased partitioning of sensitizing chemicals such as nickel that come into contact with the skin (Stefaniak *et al.,* 2012). This indicates that exposure to cobalt sulphate in refinery workers negatively impacts the integrity of the skin barrier function during a shift, allowing for possible higher cobalt absorption through the skin as proved by Larese Filon *et al* (2004). Consequently there is an increased risk of sensitisation and ultimately allergic contact dermatitis.

Biological monitoring has been proposed as a possible indicator of workers' recent exposure to cobalt, irrespective of the route of exposure. Most studies however revolve around biological monitoring of hard metal workers where good correlations were found between urine cobalt concentrations and cobalt in the air (Lison *et al*., 1994). Urine specimens were collected over a five day period to indicate the levels of cobalt present in the workers' urine. The baseline measurements indicated that five out of the 12 workers in the Cobalt plant had urine cobalt concentrations above the BEI of 15 µg/g Creatinine, with no exposure above the BEI noted in the Packaging plant workers. Baseline measurements indicated a high mean value of 17.83 µg/g Creatinine. On day 3, a slight decrease of 2.15 µg/g Creatinine was noted, followed by another decrease on Day 5 with a mean urine cobalt concentration of 12.37 µg/g Creatinine. The reason for the slight decreases cannot be fully explained. For workers in the Packaging plant, a steady increase in urine cobalt concentrations from

the baseline measurement to day 5 was observed, which indicate accumulation of cobalt during the period that packaging takes place. These levels were however much lower compared to the Cobalt plant, with means between 2.5 and 6.6 µg/g Creatinine. The lower concentrations can be explained by the work cycle of employees dedicated to this area of responsibility, where bagging operations take place approximately once every two weeks depending, on the demand for orders. More stringent PPE requirements in the Packaging plant (Tyvek® coverall suit and Drager® airstream helmets) could also have contributed to the lower urine cobalt concentrations due to the effectiveness of the PPE. Their other duties during non-bagging operations entail the packing and transport of copper sheets. Exposure periods to cobalt were also much shorter than in the Cobalt plant.

Pairwise correlations were also important to establish interactions between airborne exposure, dermal exposure and biological monitoring. These were done to get a better understanding on the metabolism of cobalt after inhalation and skin exposure, as well as to establish the efficiency of the PPE being used in the affected areas based on the urine cobalt content of the workers. In this case it was conclusive that PPE was not as effective due to the donning and doffing of gloves during the working shift. Previous studies done indicated that exposure to soluble cobalt salts produced a higher prevalence of urinary cobalt because they are absorbed better. Correlations between respiratory exposure and urine cobalt content in hard metal workers are also well documented (Linnainmaa and Kiilunen, 1997; Bucher *et al*., 1999; Krause *et al*., 2001). No correlations were found between the variables in the Cobalt plant and Cobalt and Packaging plant combined, with the exception being between average dermal exposure and the Biological monitoring (Day 3 – baseline). Strong significant positive correlations were found, meaning that dermal exposure to cobalt had an effect on the total urine cobalt content of the workers.

CONCLUSION

It is clearly evident from the results that employees are excessively exposed to high levels of inhalable cobalt via the respiratory route of exposure in both the Cobalt and Packaging plant of a base metal refinery. Skin exposure data also concluded that cobalt deposition was evident on the skin of the workers measured, with the palm of hand being the most exposed anatomical area. In conjunction with this, TEWL, skin hydration and skin surface pH measurements also indicated compromised integrity of the skin barrier function during the shift. Potential adverse health effects associated with skin exposure include sensitisation that can lead to allergic contact dermatitis in sensitive subjects. Biological urine measurements indicated that the average urine cobalt concentrations exceeded the BEI of 15µg/g Creatinine in the Cobalt plant, with lower urine cobalt concentrations detected in the Packaging plant. The high urine cobalt content associated with the workers in the Cobalt plant can be linked to their exposure times and less stringent PPE requirements as compared to the employees in the Packaging plant. Correlations to determine the contribution of each exposure route indicated only significant differences between the skin exposure data and the urine cobalt content of the employees.

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Supplementary Material

Table S1: Pair wise correlations between respiratory, dermal and urine cobalt exposures in Cobalt plant.

Variables	R-value	P-value
Cobalt Plant		
Respirable TWA vs Biological Monitoring (Day 3 – Baseline)	0.099	0.819
Respirable TWA vs Biological Monitoring (Day 3)	0.069	0.770
Inhalable TWA vs Biological Monitoring (Day 3 – Baseline)	0.500	0.267
Inhalable TWA vs Biological Monitoring (Day 3)	0.152	0.682
Dermal exposure (GM) vs Biological Monitoring (Day 3 – Baseline)	0.857	0.024
Dermal exposure (GM) vs Biological Monitoring (Day 3)	0.450	0.230
Dermal exposure (GM) vs Respirable TWA	0.344	0.271
Dermal exposure (GM) vs Inhalable TWA	0.399	0.201

Table S2: Pair wise correlations between respiratory, dermal and urine cobalt exposures in Cobalt and Packaging plant combined.

Variables	R-value	P-value
Cobalt and Packaging Plant combined		
Respirable TWA vs Biological Monitoring (Day 3 – Baseline)	0.367	0.327
Respirable TWA vs Biological Monitoring (Day 3)	0.345	0.215
Inhalable TWA vs Biological Monitoring (Day 3 – Baseline)	0.100	0.810
Inhalable TWA vs Biological Monitoring (Day 3)	0.319	0.289
Dermal exposure (GM) vs Biological Monitoring (Day 3 – Baseline)	0.867	0.005
Dermal exposure (GM) vs Biological Monitoring (Day 3)	0.368	0.217
Dermal exposure (GM) vs Respirable TWA	0.223	0.420
Dermal exposure (GM) vs Inhalable TWA	0.371	0.174

CHAPTER 4: CONCLUDING CHAPTER

This final chapter will focus on the outcome of the specific aims, objectives and hypotheses that were set for this study. All recommendations made to the base metal refinery will be based on observed methods of improvement in all stages of the hierarchy of control. The aim hereof will be to reduce respiratory and dermal exposure in both the Cobalt plant and Packaging plant. Limitations and possible future studies will also be discussed in this concluding chapter.

The first aim/objective of this study was to assess the respiratory exposure of refinery workers to cobalt sulphate. This was achieved by quantifying the respiratory exposure of refinery workers using an IOM aerosol sampler. Results indicated inhalable exposures ranging between 0.004 mg/m³ and 0.272 mg/m³, with respirable fractions ranging between 0.0002 mg/m³ and 0.0183 mg/m³. The second objective was to assess the dermal exposure of these workers to cobalt sulphate. This was also fully achieved by means of quantification of the cobalt deposition on the skin using a removal method known as Ghostwipes^{TM}. Detectable levels of cobalt were evident on the skin of exposed workers, with levels ranging between 0.104 µg/cm² and 77.600 µg/cm². Furthermore, we aimed to assess the skin barrier function by means of TEWL, skin hydration and skin surface pH measurements. This was also achieved by determining the change in skin barrier function based on measurements taken on four anatomical areas of the skin (forearm, wrist, palm of hand and back of hand) before, during and after the working shift. Another objective was to assess the workers' urine cobalt concentrations by means of biological monitoring. This was achieved by taking personal urine specimens from the workers involved and quantifying the amount of cobalt present in the urine, with levels ranging between 2.5 µg Co/g Creatinine and 17.83 µg Co/g Creatinine. The last objective was to combine all the objectives through correlations between respiratory exposure, dermal exposure and biological monitoring in order to determine the contribution of cobalt absorption via both routes of exposure. Significant strong positive correlations were found between dermal exposure and biological monitoring (Change in urine Cobalt concentration: Day 3 – Baseline) in the Cobalt plant and Cobalt and Packaging plant combined, indicating that dermal exposure contributed most to the urine cobalt

content of the workers involved. One can thus ultimately conclude that all aims and objectives have been met accordingly.

Two hypotheses were linked to this study. The first one being that workers in a Cobalt plant of a base metal refinery are exposed to cobalt sulphate through the dermal route of exposure, and based on previous literature during the subsequent packaging thereof in a Packaging plant. This hypothesis is accepted, based on the data obtained in both areas of concern where detectable levels of cobalt of between 0.104 µg/cm² and 77.600 µg/cm² were evident on the skin of exposed workers. The second hypothesis stated that workers at a base metal refinery are exposed to cobalt sulphate through the respiratory and dermal routes of exposure, which can be positively correlated with the workers' total urine cobalt concentration. This hypothesis can only be partially accepted, based on the following:

i. Respiratory exposure of workers stationed in a Cobalt and Packaging plant of a base metal refinery indicated inhalable exposures between 0.004 mg/m³ and 0.272 mg/m³, with respirable exposures only contributing a small fraction of the total respiratory exposure with results ranging from 0.0002 mg/m³ to 0.0183 mg/m³. It is thus clearly evident that workers are exposed, resulting in full acceptance of the first part of the hypothesis.
ii. Statistical correlations indicated significant strong positive correlations between dermal exposure and biological monitoring (Change in urine Cobalt concentration: Day 3 – Baseline) in the Cobalt plant and Cobalt and Packaging plants combined, indicating that dermal exposure mainly contributed to the urine cobalt content of the workers involved. No significant correlations were found between any of the remaining variable combinations, resulting in only partial acceptance of this hypothesis.

4.2. Recommendations

4.2.1. Cobalt plant

The root causes of the high exposure in the Cobalt Plant include the following:

- Failing of engineering controls to prevent spillages
- Poor production practices
- Outdated manual design of bagging operations

The following recommendations were made to assist the management of the base metal refinery to reduce their exposure in the Cobalt plant:

Recommendation 1: Use of compressed air to be substituted with a vacuum system to remove excess cobalt sulphate from the bags before transporting it to the cobalt packaging area.

Recommendation 2: Consider re-design of the bagging chute in the crystallizer section. Bags connected to the hopper chute are not sealed properly (making use of an aluminium wire to cover the chute opening) causing the cobalt sulphate to overflow/spill when the bags are too full.

Recommendation 3: Consider automating the manual valve to control the bagging of cobalt sulphate and preventing overflowing of bags when left unattended.

Recommendation 4: Crystallizer to be added to a plant maintenance schedule to ensure all bolts and flanges are always securely connected to avoid air leaks.

Recommendation 5: Consider closing and automating the manual opening system where solution is discharged into the centrifuge from the settler to avoid spillages and direct contact with the solution.

Recommendation 6: Control spillages in the dryer area by ensuring all leaking flanges and missing bolts are put on a regular plant maintenance schedule and to close the opening in the discharge from the centrifuge into the drier.

Recommendation 7: Consider automated procedures to replace the manual testing of the quality of the slurry contents in the centrifuge with wooden planks and hands.

Recommendation 8: Implement biological monitoring programme for all employees dedicated to this area of responsibility.

4.2.2. Packaging Plant

The root causes of the high exposure in the Packaging Plant include the following:

- Outdated manual design of bagging operations
- Bad housekeeping practices

The following recommendations were made to assist the management of the base metal refinery to reduce their exposure in the Packaging plant:

Recommendation 9: Consider automating the process of bagging as far as practicably possible.

Recommendation 10: Hoisting of bags from floor level to upper level to tip into the hopper requires attention as too much cobalt is being spilt and becoming airborne.

Recommendation 11: Filters in bag house on the extraction system to be replaced regularly and maintained by a set schedule.

Recommendation 12: Replace use of brooms with a vacuum system to control airborne exposures.

Recommendation 13: Implement biological monitoring programme for all employees dedicated to this area of responsibility.

4.3. Limitations and future studies

The following limitations were highlighted during the course of this study:

- Due to the small sampling group, limited biological monitoring data was obtained to fully conclude and understand the elimination of cobalt in urine.
- Varying timeframes linked to the bagging of cobalt sulphate could also have had an influence on the biological monitoring data, due to the fact that urinary levels of cobalt decrease rapidly (80-90%) within a couple of days after the last exposure.

The following inclusions can be recommended for future studies:

- Bigger sampling group with in-depth study of the elimination of cobalt in the urine of exposed workers by monitoring the timeframe between last exposure and baseline measurements closely.
- Further exploration of specific exposure in the different sections in the Cobalt plant (solvex and purification vs crystallizer).