Occupational exposure to platinum at South African precious metals refineries

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Klaagliedere 3:21 – 23

[21] Maar dit sal ek ter harte neem en om dié rede bly ek hoop: [22] deur die liefde van die Here het ons nie vergaan nie; daar is geen einde aan sy ontferming nie, [23] dit is elke môre nuut. U trou is groot.

Lamentations 3:21-23

21 *This I recall to my mind, therefore have I hope.* ***22*** *It is of the LORD's mercies that we are not consumed, because his compassions fail not.* ***23*** *They are new every morning: great is thy faithfulness.*

The thesis is dedicated to my father, Dries Linde, and my grandfathers, Oupa Attie Venter and Oupa Lou Linde, who all passed away during the past year. Thank you for the lessons in dedication and work ethic, without which I could not have completed this thesis.

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ABSTRACT

Title: Occupational exposure to platinum at South African precious metals refineries

Background: South Africa is the largest producer of platinum in the world. During the refining of platinum, complex intermediary compounds are formed, many of which are potent sensitisers. Occupational exposure to soluble platinum has been associated with the development of soluble platinum sensitisation, which is characterised by adverse effects of the respiratory system and the skin. Urinary platinum excretion has been shown to be an effective biomarker for occupational exposure to platinum and has been positively correlated with respiratory exposure. Inhalation is seen as the primary route of exposure to soluble platinum. However, the possible role of dermal exposure in the development of respiratory sensitisation has received an increasing amount of attention recently. Dermal exposure to soluble platinum and its possible correlation with platinum body burden have not previously been investigated.

Aims and objectives: The research aim of this thesis was to evaluate occupational exposure to soluble platinum of South African precious metals refinery workers and to examine the contribution of the dermal and respiratory exposure routes to the platinum body burden of workers. The specific objectives for the thesis were: (i) to conduct a critical review of the available published scientific literature on respiratory exposure to platinum group metals (PGMs) in occupational settings; (ii) to assess the platinum body burden of precious metals refinery workers through analysis of their urinary platinum excretion; (iii) to assess the respiratory exposure of precious metals refinery workers to soluble platinum using established methodology; (iv) to assess the dermal exposure of precious metals refinery workers to soluble platinum by making use of a commercially available wipe; (v) to examine the relationship between respiratory and dermal exposure to soluble platinum, and urinary platinum excretion in order to establish the contribution of each route of exposure to the platinum body burden; and (vi) to assess the effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum.

Methods: Forty workers from two South African precious metals refineries participated in this study. Dermal and respiratory exposure to soluble platinum as well as the urinary platinum excretion of workers was measured concurrently over two consecutive working days. Dermal exposure was assessed using Ghostwipes™ on four anatomical areas (palm of hand, wrist, neck and forehead) and respiratory exposure was assessed using the Methods for the Determination of Hazardous Substances (MHDS) 46/2 method. For biological monitoring, three spot urine samples were collected from each worker. The first was collected prior to the start of the first day of exposure monitoring, the second prior to the second day of exposure monitoring

and the third prior to the start of the following day's shift. Additionally surface wipe samples were also collected to examine soluble platinum surface contamination. All samples were analysed for soluble platinum according to a method based on MDHS 46/2 that uses Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). Ethics approval for the study was obtained from the Health Research Ethics Committee of the North-West University (NWU-00128-14-A1).

Results: A number of published research articles have reported occupational respiratory exposure to platinum compounds. However, the manner in which results are reported vary, which makes the comparison of results between different studies challenging. Authors often only report the number of measurements that exceeded the occupational exposure limit (OEL) of 2 µg/m^3 and do not report more detailed descriptive statistics or whether the soluble or total fraction was analysed. Analysis of the available data showed that the highest concentrations of airborne soluble platinum were reported in precious metals refineries. The degree of exposure is the greatest risk factor for the development of soluble platinum sensitisation and is influenced by a worker's area of work, the tasks performed and the fraction of soluble platinum in the workplace air. The OEL of 2 µg/m^3 has been in use since 1970. A number of studies have questioned its relevance, since sensitisation has been shown to occur at exposure below 2 µg/m^3. Furthermore, very few research articles have reported respiratory exposure to PGMs other than platinum (palladium, rhodium, iridium, ruthenium and osmium).

The results obtained from the biological and exposure monitoring studies indicated that quantifiable concentrations of soluble platinum were present in the urine of precious metals refinery workers and that workers were exposed to soluble platinum via the dermal and respiratory exposure routes. The geometric mean of the urinary platinum excretion was 0.212 µg/g creatinine [95% confidence interval (CI): 0.169-0.265 µg/g creatinine] and ranged from < 0.1 to 3.0 µg/g creatinine. The results from the three spot urine samples did not differ significantly. Significantly higher urinary platinum excretion was found for workers directly exposed to platinum compounds during production activities compared to that of non-production workers who were indirectly exposed ($p = 0.007$). The geometric mean of the average dermal exposure experienced on all four anatomical areas was 0.008 µg/cm^2 (95% CI: 0.005-0.013 µg/cm^2). The geometric mean of the respiratory exposure was 0.301 µg/m^3 (95%CI: 0.151-0.601 µg/m^3). Directly exposed workers experienced significantly higher dermal ($p = 0.002$) and respiratory ($p = 0.002$) exposure to soluble platinum. The urinary platinum excretion of workers correlated positively and significantly with their dermal exposure ($r = 0.754$) and respiratory exposure ($r = 0.580$) to soluble platinum. Detectable concentrations of soluble platinum were found on a variety of surfaces in production and non-production areas. The use of disposable coveralls and the adherence to usage procedures by workers who were directly exposed to

platinum compounds significantly reduced their dermal exposure to soluble platinum ($p = 0.018$).

Conclusions: According to the literature, the highest concentrations of airborne soluble platinum are reported in precious metals refineries. Limitations in the published body of literature investigating occupational exposure to PGMs were identified. It was clear that no standardised approach is followed for reporting respiratory exposure results which makes the comparison of studies difficult. Recommendations are made for the standardisation of the reporting methods in order to facilitate the comparison of occupational respiratory PGM exposure results from different studies in future.

The urinary platinum excretion of South African precious metals refinery workers reported in this study is comparable to that of other studies conducted in precious metals refineries in the United Kingdom, Europe and the United States of America. The urinary platinum excretion of workers showed low variability and spot urine tests can, therefore, be used to evaluate the platinum body burden of precious metals refinery workers. South African precious metals refinery workers are exposed to soluble platinum via the dermal and respiratory exposure routes and both these routes are positively correlated with the platinum body burden, as determined by urinary platinum excretion. The dermal and respiratory exposure routes should therefore be considered when investigating occupational exposure to platinum. Disposable coveralls and strict usage procedures are effective in reducing the dermal exposure of workers to soluble platinum. Finally, 19 recommendations are made to the specific precious metals refineries included in this study as well as precious metals refineries in general to reduce dermal and respiratory exposure to soluble platinum. Some limitations experienced during the study are also identified along with recommendations for future studies.

Key words: soluble platinum, dermal exposure, respiratory exposure; urinary platinum excretion, sensitisation, Ghostwipes™.

OPSOMMING

Titel: Beroepsblootstelling aan platinum by Suid-Afrikaanse edelmetaal-raffinaderye

Agtergrond: Suid-Afrika is die grootste produsent van platinum ter wêreld. Gedurende die raffineringsproses van platinum, word komplekse intermediêre verbindings gevorm waarvan heelparty kragtige sensitiseerders is. Beroepsblootstelling aan oplosbare platinum word geassosieer met die ontwikkeling van oplosbare platinum-sensitisering, wat nadelige invloede het op die asemhalingstelsel en die vel. Daar is bewys dat urinêre platinumuitskeiding 'n effektiewe biomerker is vir beroepsblootstelling aan platinum, en dat dit ook positief korreleer met respiratoriese blootstelling. Inaseming word beskou as die primêre roete waardeur blootstelling aan platinum plaasvind. Daar is tans 'n toename in belangstelling rakende die moontlike rol wat dermale blootstelling in die ontwikkeling van respiratoriese sensitisering speel. Daar is egter nog nie ondersoek gedoen na hoe dermale blootstelling aan platinum moontlik met platinumliggaamslas korreleer nie.

Doelstellings: Die navorsingsdoel van hierdie tesis was om die beroepsblootstelling van werkers by Suid-Afrikaanse edelmetaal-raffinaderye aan oplosbare platinum te evalueer en om die bydrae van dermale en respiratoriese blootstellingsroetes tot die liggaamslas van werkers te ondersoek. Die spesifieke doelstellings van die tesis, is die volgende: (i) om 'n kritiese oorsig te gee van die beskikbare gepubliseerde wetenskaplike literatuur oor respiratoriese blootstelling aan platinumgroepmetale (PGM'e) in beroepsomgewings; (ii) om die platinum-liggaamslas van edelmetaal-raffinaderywerkers te evalueer deur hul urinêre platinumuitskeiding te analiseer; (iii) om die respiratoriese blootstelling van edelmetaal-raffinaderywerkers aan oplosbare platinum aan die hand van bestaande metodologieë te evalueer; (iv) om die dermale blootstelling van edelmetaal-raffinaderywerkers aan oplosbare platinum te evalueer deur gebruik te maak van kommersieelverkrygbare velveeglappies; (v) om die verhouding tussen respiratoriese en dermale blootstelling aan oplosbare platinum, en urinêre platinumuitskeiding te ondersoek om die bydrae van elke blootstellingsroete tot die liggaamslas te bepaal; en (vi) om te bepaal hoe effektief weggooibare oorpakke daarin is om dermale blootstelling aan oplosbare platinum te verminder.

Metodes: Veertig werkers van twee Suid-Afrikaanse edelmetaal-raffinaderye het aan hierdie studie deelgeneem. Die dermale en respiratoriese blootstelling aan oplosbare platinum, asook die urinêre platinumuitskeiding van werkers is gelyktydig oor twee opeenvolgende dae gemeet. Die dermale blootstelling is geëvalueer deur gebruik te maak van velveeglappies (Ghostwipes™) op vier anatomiese areas (die palm van die hand, die gewrig, nek en voorkop). Die respiratoriese blootstelling is geëvalueer aan die hand van die MHDS (Methods for the

Determination of Hazardous Substances) 46/2-metode. Vir die biologiese monitering is drie losstaande urinemonsters by werkers geneem. Die eerste monster is voor die aanvang van die eerste dag van blootstellingsmonitering geneem, die tweede voor die tweede dag, en die derde voor die aanvang van die daaropvolgende dag se skof. Daarmee saam is monsters met veeglappies geneem om oppervlaktebesmetting deur oplosbare platinum te ondersoek. Alle monsters is vir oplosbare platinum getoets volgens 'n metode gebaseer op die MDHS 46/2-metode wat gebruik maak van induktiefgekoppelde plasma-massaspektrometrie (ICP-MS). Etiese klaring vir die studie is toegestaan deur die Gesondheidsnavorsingsetiekkomitee (HREC) van die Noordwes-Universiteit (NWU-00128-14-A1).

Resultate: 'n Aantal gepubliseerde navorsingsartikels het melding gemaak van respiratoriese beroepsblootstelling. Die manier waarop oor die resultate verslag gelewer is, verskil egter, wat dit moeilik maak om die resultate van verskillende studies met mekaar te vergelyk. Outeurs lewer dikwels slegs verslag oor die aantal metings wat die beroepsblootstellingslimiet (BBL) van 2 µg/m^3 oorskry. Hulle maak nie melding van meer gedetailleerde statistiek nie, en stel nie duidelik of die oplosbare- of totalefraksie geanaliseer is nie. Analises van die beskikbare data het aangedui dat die hoogste konsentrasies oplosbare platinum in edelmetaal-raffinaderye te vind is. Die vlak van blootstelling is die ernstigste risikofaktor betrokke by die ontwikkeling van sensitisering vir oplosbare platinum en word beïnvloed deur 'n werker se werksarea, die take wat uitgevoer word en die fraksie van oplosbare platinum in die lug van die werksplek. Die BBL van 2 µg/m^3 is reeds vanaf 1970 in gebruik. 'n Aantal studies het al die relevansie daarvan bevraagteken aangesien daar bewys is dat sensitisering ook plaasvind teen blootstellings wat onder 2 µg/m^3 is. Min artikels lewer verslag oor respiratoriese blootstelling aan ander PGM'e as platinum (soos palladium, rodium, iridium, rutenium en osmium).

Die resultate van die biologiese- en blootstellingsmonitering het aangedui dat kwantifiseerbare konsentrasies oplosbare platinum in die urine van edelmetaal-raffinaderywerkers te vind is en dat werkers aan oplosbare platinum blootgestel word via dermale en respiratoriese roetes. Die meetkundige gemiddelde van die urinêre platinumuitskeiding was 0.212 µg/g kreatinien [95% vertrouensinterval (CI): 0.169-0.265 µg/g kreatinien] en het gestrek van < 0.1 tot 3.0 µg/g kreatinien. Die resultate van die drie losstaande urinemonsters het nie in 'n betekenisvolle mate verskil nie. In vergelyking met nie-produksie werkers wat op indirekte wyse blootgestel is, is aansienlik hoër urinêre platinumuitskeiding gevind by werkers wat gedurende produksieaktiwiteite direk aan platinumverbindings blootgestel is ($p = 0.007$). Die meetkundige gemiddelde van die dermale blootstelling wat ervaar is op al vier anatomiese areas (as gemiddeld), was 0.008 µg/cm^2 (95% CI: 0.005-0.013 µg/cm^2). Die meetkundige gemiddelde van die respiratoriese blootstelling was 0.301 µg/m^3 (95%CI: 0.151-0.601 µg/m^3). Werkers wat direk blootgestel is, het aansienlik hoër dermale ($p = 0.002$) en respiratoriese blootstelling ($p = 0.002$)

tot oplosbare platinum ervaar. Die urinêre platinumuitskeiding van die werkers het betekenisvol gekorreleer met hulle dermale blootstelling (r = 0.754) en respiratoriese blootstelling (r = 0.580) tot oplosbare platinum. Waarneembare konsentrasies oplosbare platinum is op 'n verskeidenheid oppervlaktes in produksie- en nie-produksieareas gevind. Werkers wat direk blootgestel is aan platinumverbindings, wat gebruik gemaak het van weggooibare oorpakke en die prosedures van die werksarea nagekom het, se dermale blootstelling tot oplosbare platinum was aansienlik minder (p = 0.018).

Gevolgtrekkings: Die hoogste konsentrasies luggedrae oplosbare platinum kan volgens die literatuur in edelmetaal-raffinaderye gevind word. Tekortkominge is geïdentifiseer in die gepubliseerde korpus van navorsing oor beroepsblootstelling aan PGM'e. Dit is duidelik dat daar geen gestandaardiseerde benadering gevolg word wanneer oor die resultate van respiratoriese blootstelling gerapporteer word nie, wat dit moeilik maak om studies met mekaar te vergelyk. Aanbevelings is gemaak rakende die standaardisering van rapporteringsmetodes sodat vergelyking van resultate van respiratoriese beroepsblootstelling tot PGM'e vergemaklik kan word met die oog op toekomstige studies.

Die urinêre platinumuitskeiding van Suid-Afrikaanse edelmetaal-raffinaderywerkers wat in hierdie studie vermeld word, is vergelykbaar met dié van ander studies wat in edelmetaal-raffinaderye in die Verenigde Koninkryk, Europa en die Verenigde State van Amerika gedoen is. Die urinêre platinumuitskeiding van werkers het min veranderlikheid getoon wat daarop dui dat alleenstaande urinemonsters met vrug gebruik kan word om die platinumliggaamslas van edelmetaal-raffinadery-werkers te evalueer. Suid-Afrikaanse edelmetaal-raffinaderywerkers word blootgestel aan oplosbare platinum via die dermale en respiratoriese blootstellingsroetes. Beide hierdie roetes korreleer positief met die platinumliggaamslas soos bepaal deur die urinêre platinumuitskeiding. Die dermale en respiratoriese roetes moet daarom in ag geneem word wanneer beroepsblootstelling aan platinum ondersoek word. Weggooibare oorpakke en streng gebruiksprosedures kan die dermale blootstelling van werkers aan oplosbare platinum effektief verminder. Laastens is daar 19 aanbevelings gemaak aan die spesifieke edelmetaal-raffinaderye wat in hierdie studie ter sprake kom sowel as aan edelmetaal-raffinaderye in die algemeen rakende maniere waarop dermale en respiratoriese blootstelling aan oplosbare platinum verlaag kan word. Sekere beperkinge is gedurende hierdie studie ervaar en aanbevelings vir verdere studie, is ook gemaak.

Sleutelwoorde: oplosbare platinum, dermale blootstelling, respiratoriese blootstelling, urinêre paltinumuitskeiding, sensitisering, Ghostwipes™.

PREFACE

This thesis is submitted in article format and written according to the requirements of the North-West University's Manual for Postgraduate Studies and conforms to the requirements preferred by the appropriate journals. The thesis is written according to United Kingdom English spelling, with the exception of institutional names and references that were used as is. The following four articles are included in this thesis:

- Article I: Occupational respiratory exposure to platinum group metals: A review and recommendations.
- Article II: Urinary excretion of platinum from South African precious metals refinery workers.
- Article III: Biological monitoring of platinum following dermal and respiratory exposure to soluble platinum at South African precious metals refineries.
- Article IV: Effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum.

For uniformity, the reference style required by the journal *Annals of Work Exposures and Health* is used throughout the thesis. The author instructions for this journal are located in the beginning of Chapter 6. The exceptions are Chapter 3, Chapter 4 and Chapter 5 which are written according to the guidelines of *Chemical Research in Toxicology, Occupational and Environmental Medicine* and *Contact Dermatitis,* respectively. Details on the requirements of reference styles can be found in the beginning of Chapters 4, 5 and 6 of this thesis.

The contributions of the listed co-authors and their consent for use in this thesis are given in Table 1. The relevant editors or publishers granted permission for the use of the published material. Proof of the permission is given Appendix A.

Table 1: Contributions of various authors and consent for use

Author	Contribution to the thesis	Consent*
Mr. S.J.L. Linde	Responsible for the planning of the study design and the data collection. Responsible for data collection by performing exposure and biological monitoring studies at the respective precious metals refineries. Responsible to data analysis and interpretation of the results. First author of the articles included in Chapters 3 – 6. Responsible for writing the thesis	
Prof. J.L. du Plessis	As Promoter, supervised the design and planning of the study as well as the data collection and the writing of the thesis. Secured the funding for the study as well as the participation of the respective precious metals refineries. Provided intellectual input on statistical analysis, interpretation of data and the writing of articles and the thesis.	
Prof. A. Franken	As Co-promoter, supervised the design and planning of the study as well as the data collection and the writing of the thesis. Provided intellectual input on statistical analysis, interpretation of data and the writing of articles and the thesis.	

* I declare that I have approved the manuscript and that my role in the study, as indicated in Table 1, is representative of my actual contribution. I hereby give my consent that this manuscript may be published as part of the PhD thesis of Mr. S.J.L. Linde.

The outline of this thesis is as follows:

- Chapter 1: General introduction with background, research aims and objectives, and hypotheses.
- Chapter 2: Literature study on the topics relevant to this thesis.
- Chapter 3: Article I: Occupational respiratory exposure to platinum group metals: A review and recommendations, published in *Chemical Research in Toxicology.*
- Chapter 4: Article II: Urinary excretion of platinum from South African precious metals refinery workers, submitted for publication in *Occupational and Environmental Medicine*.
- Chapter 5: Article III: Biological monitoring of platinum following dermal and respiratory exposure to soluble platinum at South African precious metals refineries, submitted for publication in *Contact Dermatitis*.
- Chapter 6: Article IV: Effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum. This article is to be submitted for publication in *Annals of Work Exposures and Health*.
- Chapter 7: A summary of the main findings of the study is provided and conclusions are drawn. Additionally, recommendations are made, and the limitations of the study as well as recommendations for future studies are provided.
- Appendix A: Permission to use copyright material.
- Appendix B: Proof of submission of articles II and III to the respective scientific journals.
- Appendix C: Declaration of language editing.

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"Any opinion, finding, conclusion and recommendation expressed in this material is that of the author(s), and the NRF does not accept any liability in this regard."

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µg/m^3	microgram per cubic metre
oz	ounce
g	gram
l/min	litre per minute
ml	millilitre
pg/m^3	picogram per cubic metre
PM_{10}	particulate matter 10 micrometres or less in aerodynamic diameter
ng/l	nanogram per litre
µg/l	microgram per litre
n	number
µg/g creatinine	microgram per gram of creatinine
µg/kg	microgram per kilogram
ng/g	nanogram per gram
mg	milligram
µg Pt/l	microgram platinum per litre
η^2	partial eta-squared
µg Pt/g creatinine	microgram of platinum per gram of creatinine
g	gram
r	regression coefficient
µg/cm^2	microgram per centimetre squared
cm	centimetre
cm^2	centimetre squared

LIST OF ABBREVIATIONS

≤	less than or equal to
<	less than
>	more than
AAS-GF	graphite furnace atomic absorption spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists, United States of America (USA)
ANCOVA	analysis of covariance
ANCOVA	analysis of variance
AM	arithmetic mean
BEI®	biological exposure indice
CDC	Centres for Disease Control and Prevention, USA
Cis Pt(II)	cisplatin
CI	confidence interval
CO	carbon monoxide
CO_2	carbon dioxide
DECOS	Dutch Expert Committee on Occupational Standards, The Netherlands
DMR	Department of Minerals and Resources, South Africa
DFG	Deutsche Forschungsgemeinschaft , Germany
DOL	Department of Labour, South Africa
Eds.	editors
et al.	*et alii* (and others)
EC SCOEL	European Commission Scientific Committee on Occupational Exposure Limits, European Union
Eurometaux	European Association of Metals

LIST OF ABBREVIATIONS (CONTINUED)

FFP_2	filtering facepiece 2
GM	geometric mean
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
h	hour
HSE	Health and Safety Executive
ICMM	International Council on Mining and Metals
ICP-AES	inductively coupled plasma-atomic emission spectroscopy
ICP-MS	inductively coupled plasma-mass spectrometry
IOM	Institute for Occupational Medicine, United Kingdom
IPA	International Platinum Group Metals Association
IPCS	International Programme on Chemical Safety
Ig	immunoglobulin
Il	interleukin
Ir	iridium
ISO	International Organization for Standardization
ISO-TR	International Organisation for Standardisation's (ISO) Technical report
$K_2[Pt(NO_2)_4$	potassium tetranitroplatinate(II)
JSOH	Japan Society for Occupational Health, Japan
LOD	limit of detection
MDHS	Methods for the Determination of Hazardous Substances
MCE	mixed cellulose ester
$Na_2Pt(IV)I_6$	sodium hexahydroxyplatinate(IV)

LIST OF ABBREVIATIONS (CONTINUED)

$NaBH_4$	sodium borohydride
$(NH_4)_2PtCl_6$	ammonium hexachloroplatinate
$NH_4)_2[PtCl_4]$	ammonium tetrachloroplatinate
NIOSH	National Institute for Occupational Health and Safety
NO_x	nitric oxides
NRF	National Research Foundation of South Africa
OEL	occupational exposure limit
Os	Osmium
OSHA	Occupational Safety and Health Administration, USA
p	p-value
PEL	permissible exposure limit
PGM	platinum group metal
Pd	palladium
Pt	platinum
$PtAl_2O_3$	oxo(oxoalumanyloxy)alumane platinum
$PtCl_2$	platinum(II)chloride
$PtCl_4$	platinum tetrachloride
PPE	personal protective equipment
PVC	poly vinyl chloride
r	regression coefficient
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals

LIST OF ABBREVIATIONS (CONTINUED)

Rh	rhodium
RPE	respiratory protective equipment
Ru	ruthenium
Sk	skin notation
Sen	sensitiser notation
SO_x	sulphur oxides
TPC	tetraammine platinum trichloride
TWA	time-weighted average
TLV® -TWA	threshold limit value-time weighted average
UK	United Kingdom
URL	uniform resource locator
US	United States
USA	United Stated of America
WHO	World Health Organisation
WEL	workplace exposure limit

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CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction

Platinum group metals (PGMs) is a group of rare metals which includes platinum, palladium, rhodium, ruthenium, iridium and osmium (Macdonald, 1982). South Africa is the largest producer of PGMs in the world and, in 2016, supplied 72% (4 392 000 oz) of the world's platinum, 38.1% (2 574 000 oz) of the world's palladium and 79.5% (615 000 oz) of the world's rhodium (Johnson Matthey, 2017). In 2016, the South African PGM sector employed over 172 310 employees (Chamber of Mines of South Africa, 2017) and some of these workers are at risk of experiencing the adverse health effects associated with occupational PGM exposure. Secondary industries such as automotive catalyst production, bulk-chemical production, petroleum refining, electronics manufacturing and jewellery fabrication utilise these precious metals and workers in these industries are also potentially exposed to PGMs (Kielhorn *et al.,* 2002; Xiao and Laplante, 2004; Chamber of Mines of South Africa, 2017).

The adverse health effects associated with exposure to platinum compounds are more evident during refining, as this is where PGMs are concentrated and eventually separated to produce the individual precious metal commodities (Kielhorn *et al.,* 2002). During the refining process, PGMs are concentrated and separated using precipitation and dissolution techniques with many complex intermediary compounds being formed. Of these compounds, the chloroplatinates are of the greatest importance to health as they are potent sensitisers (WHO, 2000; Bencs *et al.,* 2011) and numerous studies have indicated that they cause sensitisation by means of Type I hypersensitivity reactions (Cleare *et al.,* 1976; Niezborala and Garnier 1996; Linnett and Hughes, 1999). This thesis focuses on platinum, especially soluble platinum compounds, since they are considered to be most hazardous to the health of workers (Linnett and Hughes, 1999).

The adverse health effects caused by soluble platinum include respiratory conditions and/or symptoms such as asthma, rhinitis and tightness of the chest as well as skin conditions such as allergic contact dermatitis and eczema (Hunter *et al.,* 1945; Merget *et al.,* 2000; Cristaudo *et al.,* 2005). Toxic effects following occupational exposure to soluble platinum were first reported in 1911 in a photographic studio (Karasek and Karasek, 1911) and asthma caused by exposure to soluble platinum in precious metals refineries was first reported in 1945 (Hunter *et al.,* 1945). Since then, numerous studies have investigated soluble platinum hypersensitivity in occupational settings (Calverley *et al.,* 1995; Linnett and Hughes, 1999; Merget *et al.,* 2000; Cristaudo *et al.,* 2005; Heederik *et al.,* 2016). It is estimated that 1% of exposed workers are sensitised annually even though exposure to soluble platinum is generally contained below the

respiratory occupational exposure limit (OEL). Following sensitisation to soluble platinum, the sensitised worker is permanently removed from any exposure and is often removed from employment within the platinum industry (Bullock, 2010).

Inhalation is considered to be the major route for occupational exposure to platinum compounds (Kiilunen *et al.,* 2015) and many studies have concluded that the development of soluble platinum sensitisation is associated with the intensity of a worker's exposure to soluble platinum (Calverley *et al.,* 1995; Merget *et al.,* 2000; Heederik *et al.,* 2016). Increased respiratory exposure to soluble platinum has been shown to occur during the direct handling of platinum compounds during production activities (Hunter *et al.,* 1945; Cristaudo *et al.,* 2007). The exact exposure circumstances that cause sensitisation, however, are not yet known and the exposure threshold that causes sensitisation has not yet been established (Bullock, 2010). Most countries, including South Africa, impose an 8-hour time-weighted average (TWA) respiratory exposure limit of 2 µg/m^3 for soluble platinum compounds. This is regarded as one of the lowest limits for workplace respiratory chemical exposure (Bullock, 2010; DMR, 2017; DOL, 2017).

The majority of occupational exposure studies focuses solely on respiratory exposure (Calverley *et al.,* 1995; Linnett and Hughes, 1999; Merget *et al.,* 2000; Kielhorn *et al.,* 2002; Violante *et al.,* 2005) and subsequently, there is no indication of the actual levels of dermal exposure in occupational settings. This is surprising, since a number of skin related symptoms and conditions have been reported following occupational exposure to soluble platinum (Hunter *et al.,* 1945; Merget *et al.,* 2000). Maynard *et al.* (1997) reported that sensitisation occurred in platinum industries (including precious metals refineries) where the airborne soluble platinum concentrations were well below the OEL. They suggested that another route of exposure, other than respiratory exposure, might be responsible for sensitisation. Because they observed significant skin contact with soluble platinum during their investigations, they proposed that dermal exposure could possibly contribute to sensitisation. Additionally, very low amounts of soluble platinum have been reported to permeate through intact human skin during *in vitro* experiments which confirmed the dermal exposure route as a relevant route for exposure to soluble platinum (Franken *et al.,* 2014). Linnett and Hughes (1999) concluded that infrequent dermal exposure could lead to high levels of soluble platinum on the skin, contributing to, or causing, sensitisation or alternatively that sensitisation is due to respiratory exposure to very low levels of soluble platinum. It is, therefore, unclear whether respiratory exposure, dermal exposure or a combination of respiratory and dermal exposure may be involved in sensitisation and the possible elicitation of respiratory and skin symptoms. For this reason, it is important to establish whether workers at precious metals refineries are exposed to platinum through the dermal route of exposure and at what concentrations. The reporting of dermal exposure to

soluble platinum will also contribute to the growing body of literature available on dermal exposure to sensitising metals in occupational settings which is currently primarily limited to beryllium, cobalt, chromium, lead and nickel (Hughson *et al.,* 2005; Lidén *et al.,* 2006; Day *et al.,* 2009; Du Plessis *et al.,* 2010; Hughson *et al.,* 2010; Julander *et al.,* 2010; Du Plessis *et al.,* 2013; Klasson *et al.,* 2017).

Biological monitoring involves the assessment of human exposure to chemical substances through the measurement of internal concentrations of the chemical itself, its metabolite or another type of biochemical change caused by exposure to the chemical (AIHA, 2004). It can assist with the identification of the most evident route of exposure contributing to total exposure, as it determines total exposure of an individual to a chemical by accounting for all routes of exposure (Angerer *et al.,* 2007). Urinary platinum excretion is considered an efficient biomarker for occupational monitoring (Petrucci *et al.,* 2005) and numerous studies have successfully used urine as biological matrix to determine workers' occupational exposure to platinum compounds (Schaller *et al.,* 1992; Schriel *et al.,* 1998; Petrucci *et al.,* 2005; Cristaudo *et al.,* 2007; Iavicoli *et al.,* 2007). Inhalation exposure to soluble platinum compounds experienced by previously non-exposed volunteers has been shown to increase their urinary platinum excretion by up to 100-fold compared to before exposure (Schriel *et al.,* 1998). Platinum body burden is closely associated with the airborne platinum concentration in work areas (Petrucci *et al.,* 2005; Cristaudo *et al.,* 2007) but no information is available on the effect of dermal exposure on platinum body burden. Biological monitoring is of considerable importance when it comes to determining an individual's exposure to platinum (Iavicoli *et al.,* 2007) and for establishing if dermal exposure is a significant contributor to the worker's overall exposure (Klasson *et al.,* 2017). For example, in a work environment where the respiratory exposure to a specific chemical is well controlled, or well characterised, an abnormally elevated biological monitoring result will likely indicate that dermal exposure or ingestion is a major route of exposure (OSHA, 2011). Biological monitoring in the form of urinary platinum excretion has been reported for precious metal refineries in Europe, the United Kingdom (UK) and the United States of America (USA) (Johnson *et al.*, 1976; Farago *et al.,* 1998; Schierl *et al.,* 1998) but not yet for South Africa, the largest producer of platinum in the world (Johnson Matthey, 2017).

In order to properly assess biological monitoring findings, respiratory and dermal exposure assessments must also be conducted to determine the sources of the exposure and the most likely routes of entry of the chemical substances into the body (OSHA, 2011). Recently, biological monitoring has been used in conjunction with respiratory and dermal exposure results to demonstrate that the dermal route of exposure could possibly affect the uptake of cobalt into the body in the same order of magnitude as respiratory exposure (Klasson *et al.,* 2017). This

information changed the methods applied by employers in the hard metal industry to control workers' exposure to cobalt. No published information is available on the contribution of dermal exposure to the platinum body burden of workers exposed to soluble platinum compounds. In fact, there is no published information available on the dermal exposure to soluble platinum experienced by workers in any occupational setting. It is, therefore, of particular importance to quantify the dermal and respiratory exposure of precious metals refinery workers to soluble platinum in order to assess the contribution of each route of exposure to the platinum body burden.

This thesis aims to assess the occupational exposure to soluble platinum experienced by South African precious metals refinery workers as well as to examine the relationship between the respiratory and dermal exposure routes in contributing to the platinum body burden of workers. Awareness of the contribution of respiratory and dermal exposure routes to the platinum body burden could improve the approach of management to control the precious metals refinery workers' exposure to soluble platinum and allow them to improve the health of their workers.

1.2 Research aims and objectives

1.2.1 General aim

The general aim of this thesis is to evaluate respiratory and dermal exposure to soluble platinum of South African precious metals refinery workers and to examine the contribution of each of these routes of exposure to the platinum body burden of workers, as determined by their urinary platinum excretions.

1.2.2 Specific objectives

The specific objectives of this thesis are:

i. to conduct a critical review of the available published scientific literature on respiratory exposure to PGMs in occupational settings.
ii. to assess the platinum body burden of precious metals refinery workers through analysis of the platinum concentration present in their urine of the workers.
iii. to assess the respiratory exposure of precious metals refinery workers to soluble platinum using the *Methods for the Determination of Hazardous Substances* (MDHS) 46/2 method (HSE, 1996).
iv. to assess the dermal exposure of precious metals refinery workers to soluble platinum by making use of a commercially available wipe.
v. to examine the relationship between respiratory and dermal exposure to soluble platinum, and urinary platinum excretion in order to establish the contribution of each route of exposure to the platinum body burden.
vi. to assess the effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum.

1.3 Hypotheses

The following hypotheses are postulated:

i. Published biological monitoring studies performed in Europe, the UK and the USA have reported urinary platinum excretion from precious metals refinery workers in the range of < 0.1 to 6.270 µg/g creatinine (Johnson *et al.*, 1976; Farago *et al.,* 1998; Schierl *et al.,* 1998). It is hypothesised that the urinary platinum excretion of workers from South African precious metals refineries is comparable to that of precious metals refinery workers from other countries.

ii. Precious metals refinery workers who directly handle platinum compounds have been shown to experience increased exposure to soluble platinum (Hunter *et al.,* 1945). Additionally, the urinary platinum excretion of automotive catalyst production workers have been positively correlated with respiratory exposure to platinum compounds (Cristaudo *et al.,* 2007). It is, therefore, hypothesised that precious metals refinery workers who are directly exposed to platinum compounds have significantly increased urinary platinum excretion compared to workers who are indirectly exposed.

iii. Published occupational exposure studies have shown that precious metals refinery workers are exposed to soluble platinum via the respiratory pathway (Calverley *et al.,* 1995; Heederik *et al.,* 2016) and it has been suggested that the dermal route of exposure might serve as an alternative route for exposure to soluble platinum (Maynard *et al.,* 1997; Heederik *et al.,* 2016). It is, therefore, hypothesised that South African precious metals refinery workers are exposed to soluble platinum via the respiratory exposure route and that detectable concentrations of soluble platinum are present on the skin of workers, which is indicative of dermal exposure.

iv. It has been demonstrated that for certain other metals both the respiratory and dermal exposure pathways contribute to the body burden (ICMM, 2007; Klasson *et al.,* 2017). Increased platinum body burden has been associated with high respiratory exposure to soluble platinum (Cristaudo *et al.,* 2007) and very low amounts of soluble platinum have been shown to permeate through intact human skin (Franken *et al.,* 2014). It is, therefore, hypothesised that respiratory and dermal exposure of South African precious metals refinery workers to soluble platinum correlates positively with their platinum body burden (as reflected by the urinary platinum excretion).

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CHAPTER 2: LITERATURE STUDY

2.1 Introduction

This chapter contains a critical discussion of the available scientific literature related to occupational exposure to platinum. Information on the physical and chemical properties of platinum is provided. Also, the applications of platinum and the industries where workers may be exposed to platinum compounds are described, with the emphasis on precious metals refineries. This is followed by an analysis of the occupational exposure experienced by workers via the respiratory and dermal pathways as well as the methods used to assess exposure. Additional to occupational exposure, environmental exposure to platinum compounds is also briefly mentioned. Next, the role of biological monitoring in exposure assessment as well as its application in determining the total body burden of platinum is deliberated. This is followed by a summary of the absorption, distribution and elimination of platinum in humans as well as a description of the adverse health effects associated with exposure. Finally, the applicable legislation regarding occupational exposure to platinum compounds is presented. Chapter 3 of this thesis contains a review article published in *Chemical Research in Toxicology* (Linde *et al.*, 2017), which critically analyses and summarises published literature regarding the occupational respiratory exposure to platinum group metals. Occupational respiratory exposure to platinum group metals (PGMs) is, therefore, only briefly discussed in this chapter.

2.1.1 Physical and chemical properties

Platinum was first discovered in the Choco District of Colombia in the 16th century and is the most important of the PGMs, which includes platinum, palladium, rhodium, iridium, ruthenium and osmium (Macdonald and Hunt, 1982). Platinum is a silvery white lustrous metal which is ductile, malleable, and resistant to corrosion and oxidation. It also has a high melting point as well as good electrical conductivity and catalytic activity (Xiao and Laplante, 2004). Platinum metal is known to catalyse many oxidation-reduction and decomposition reactions (U.S. Department of Health and Human Services, 2015). Platinum complexes are most stable at the +2 and +4 oxidation states and has a maximum oxidation state of +6. Platinum often forms part of coordination complexes such as hexachloroplatinic acid, cis- and trans-diamminedichloroplatinum, potassium and ammonium tetrachloroplatinate and potassium, sodium and ammonium hexachloroplatinate (WHO, 2000).

2.1.2 Supply, demand and uses

South Africa is the world's leading producer of platinum, followed by Russia, Canada and Zimbabwe. In 2016, South Africa supplied 4 392 000 oz of platinum, which constituted 72% of the world's total primary platinum supplies (Johnson Matthey, 2017). PGMs accounted for approximately 21% of South Africa's total commodity sales in 2016 and approximately 172 310 workers were employed in the PGM mining sector during the same year (Chamber of Mines of South-Africa, 2017).

Platinum is valuable for its wide range of industrial applications in the automotive, chemical, electronics, chemical, jewellery and petroleum industries (Xiao and Laplante, 2004; Chamber of Mines of South-Africa, 2017). Platinum is used as catalysts during chemical reactions such as hydrogenation, isomerisation, cyclisation, dehydration, dehalogenation and oxidation (WHO, 2000). The demand for platinum is especially high in the automotive industry where it, along with other PGMs, is used to convert noxious gasses into more benign forms (Wiseman and Zereini, 2009). The demand for platinum, along with other PGMs, for application in automotive catalytic converters is set to increase due to stricter emission standards for automotive vehicles and this trend is expected to continue (Chamber of Mines of South-Africa, 2017). In 2016, the demand for platinum in the automotive catalyst industry was 3 318 000 oz with the greater part (1 778 000 oz) being used in Europe. The increase in the demand for platinum in Europe resulted from Euro 6b legislation which mandated a 56% reduction in the emissions of nitric oxides (NO_x) compared to the previous legislation. This is achieved by implementing after-treatment systems such as platinum-rich lean NO_x traps and PGM-coated diesel particulate filters (Johnson Matthey, 2017).

In 2016, the demand for automotive catalysts was at an eight-year high and the demand for platinum in industrial applications was at its maximum level in five years (Johnson Matthey, 2017). These statistics is a clear indication that platinum is in highly demanded in various industries, especially the automotive industry. The satisfaction of this demand will lead to even more workers employed in the mining, refining and secondary production industries being exposed to platinum compounds and risking the development of adverse health effects associated with exposure.

2.1.3 Types of industries

PGM production requires the processing of platinum ore, followed by the extraction and refining of the concentrate to obtain separate pure PGMs (Utembe *et al.*, 2015). Occupational exposure to chloride-containing platinum compounds such as tetrachloroplatinates and hexachloroplatinates during these mining and refining activities, as well as during the

processing of platinum compounds, can lead to allergic responses of the airways and the skin (Cleare *et al.*, 1976; EC SCOEL, 2011). For that reason, the processes associated with platinum mining, refining and processing are discussed in the following section. Special attention is given to specific instants in these processes where allergy eliciting platinum compounds could be generated to obtain an understanding of how exposure might take place.

2.1.3.1 Mining and refining of platinum

Platinum can be found, along with other PGMs, in very low concentrations in the earth's crust (Ravindra *et al.*, 2004). Because of their low natural occurrence and the complexities associated with their extraction and refining, PGMs are very rare compared to other precious metals such as gold. The concentration of PGMs in South African deposits is less than 10 g per ton ore (approx. 50-60% platinum and 20-25% palladium) (Bernardis *et al.*, 2005; Seymour and O'Farrelly, 2012).

The first economic deposits of platinum were discovered in South Africa in 1924 and most of the country's available reserves are concentrated in the geological area which is known as the Bushveld Igneous Complex (Jones, 1999; Seymour and O'Farrelly, 2012). The ore of the Bushveld Igneous Complex is associated with base metal sulphide minerals. After the ore has been mined, comminution takes place and a gravity concentrate is extracted after which the sulphides are concentrated through floatation (Jones, 1999). The concentration process aims to concentrate the mined ore into a material which contains approximately 60% PGMs (Seymour and O'Farrelly, 2012). The concentrate is then smelted and converted into PGM containing nickel-copper matte which is then hydrometallurgically treated to separate the base metals. Finally, the PGM concentrate is refined to produce pure individual PGMs (Jones, 1999). Since this thesis provides information on occupational exposure to soluble platinum during refining, the refining process of platinum is discussed further in the section below, with specific focus on the potential opportunities for exposure to soluble platinum compounds.

Most refineries use a combination of the conventional precipitation refining process and solvent extraction refining process (Liddell *et al.*, 1986; Seymour and O'Farrelly, 2012). The conventional refining process is a combination of complex selective dissolution and precipitation techniques (Seymour and O'Farrelly, 2012). Firstly, aqua regia (a mixture of concentrated nitric and hydrochloric acids) is added to the concentrate which dissolves most of the platinum and palladium but leaves the other more insoluble PGMs as residues. Next, the platinum containing solution is treated with ammonium chloride and an ammonium hexachloroplatinate precipitate is produced (Liddell *et al.*, 1986; Seymour and O'Farrelly, 2012). The ammonium hexachloroplatinate precipitate is then recovered using filter presses and glove boxes and transported to furnaces for calcination (Seymour and O'Farrelly, 2012). It is during this stage of

the refining process that the highest risk for exposure to soluble platinum exists. Workers often need to handle the ammonium hexachloroplatinate precipitate (in salt form) in order to remove it from the filter presses or glove boxes and to transport it to the furnaces for calcination. Calcination of the precipitate produces a platinum sponge which is either melted to produce bars or crushed into specific sizes and packaged according to the needs of the buyer (Seymour and O'Farrelly, 2012).

The solvent extraction process involves three steps namely, extraction (extracting a specific metal from the PGM-stream), scrubbing (removing unwanted metals or other materials from the selected metal) and stripping (removing the extracted metal from the organic phase). The solvent extraction process in characterised by a higher selectivity compared to the precipitation method and allows for increased metal purity. Additionally, the precipitation method results in a lower separation efficiency which requires repeated washing and filtration stages (Bernardis *et al.*, 2005; Seymour and O'Farrelly, 2012). The two precious metals refineries included in this thesis rely primarily on precipitation techniques to refine PGMs. A brief outline of the work areas included in this study and their function in the refining process is provided in the supplementary material of Chapter 4 of this thesis.

2.1.3.2 Secondary industries and recycling

The worldwide demand for automotive catalysts and the industrial consumption of platinum by the glass and chemicals industries is increasing (Johnson Matthey, 2017). Automotive catalysts are used to reduce the emissions of residual uncombusted hydrocarbons, carbon monoxide (CO), NO_x, particulate matter and carbon dioxide (CO_2) from internal combustion engines (Shelef and McCabe, 2000). During the production of catalytic converters, PGM sponge is solubilised into PGM solutions which can then be used to coat catalysts by dispersing the PGM solution onto ceramic or metal honeycomb supports (Dewar, 2012; Seymour and O'Farrelly, 2012). PGMs are used as active catalytic materials because they dispose of the necessary reactivity to remove pollutants in the very short space and residence times available, they are resistant to poisoning by residual amounts of sulphur oxides (SO_x) in the exhaust and they are less prone to deactivation by high temperature interaction with the insulator oxides of aluminium, cerium and zirconium. Mostly combinations of platinum, palladium and rhodium are used as automotive catalysts since they display different catalytic properties (Shelef and McCabe, 2000). For example, platinum is a very effective converter of CO and hydrocarbons but does not reduce NO_x, while rhodium is very effective at reducing NO_x (Seymour and O'Farrelly, 2012).

Platinum is used in the chemical industry to catalyse reactions such as hydrogenation, oxidation, dehydrogenation and hydrogenolysis. It is often used to manufacture chemicals such

as nitric acid and to control emissions or to destroy volatile organic compounds during incineration (Seymour and O'Farrelly, 2012).

Along with mining, the PGM recycling industry in 2016 also contributed to the worldwide supply of platinum with 1 922 000 oz. being recovered from spent automotive catalysts, jewellery, electronics and gasoline scrap (Johnson Matthey, 2017). During recycling, the PGM containing materials are dissolved in aqua regia to form PGM chloro-complexes which is then converted into metallic PGMs (Seymour and O'Farrelly, 2012).

Substantial occupational exposure to platinum compounds has been shown to take place during the production of automotive catalysts and during recycling of platinum products (Merget, 2000; Cristaudo *et al.,* 2007; Kiilunen *et al.,* 2015). However, since this thesis focuses on occupation exposure to platinum during platinum refining, the processes associated with the production of automotive catalysts and recycling of platinum material will not be discussed further. For further reading, please refer to review articles by Dewar (2012) and Shelef and McCabe (2000).

2.1.3.3 Medical industry

In the medical industry, platinum containing chemotherapeutic drugs such as cis-platin, carboplatin and oxaliplatin are used during chemotherapy (Schmaus *et al.,* 2002; Klopp *et al.,* 2013; Kiilunen *et al.,* 2015). However, the use and exposure to platinum containing chemotherapeutic drugs and their analogues fall outside the scope of this thesis and will not be discussed further. For further reading, please refer to articles by Schmaus *et al.* (2002) and Klopp *et al.* (2013), as well the chapter on platinum (Kiilunen *et al.,* 2015) in the *Handbook on the toxicology of metals, volume II* (Nordberg *et al.,* 2015).

2.2 Occupational exposure

Occupational exposure to soluble platinum is associated with respiratory and dermal adverse health effects (Hunter *et al.,* 1945; Cristaudo *et al.,* 2005; Heederik *et al.,* 2016). Respiratory exposure to soluble platinum experienced by workers in various occupational settings, such as precious metals refineries, automotive catalyst production plants and recycling industries, has been reported by a number of studies (Hunter *et al.,* 1945; Maynard *et al.,* 1997; Petrucci *et al.,* 2005; Cristaudo *et al.,* 2007; Heederik *et al.,* 2016). The dermal exposure to soluble platinum experienced by workers, on the other hand, has not yet been investigated and reported, although dermal exposure to other metals has been reported in various occupational settings. These include, base metals refineries (Du Plessis *et al.*, 2010), nickel refineries and primary nickel user industries (Hughson *et al.*, 2010), lead refineries (Hughson, 2005), hard metal production plants (Midander *et al.*, 2014; Klasson *et al.*, 2017), cemented tungsten carbide

production plants (Day *et al.*, 2009), the space propulsion industry (Julander *et al.*, 2010) and the dental industry (Kettelarij *et al.*, 2016).

2.2.1 Respiratory exposure

Literature regarding occupational respiratory exposure to soluble platinum, as well as that of other PGMs, is reviewed in detail in Chapter 3 of this thesis. In this review article, available information regarding respiratory exposure to PGMs in various occupational settings is summarised and it is shown that the highest concentrations of airborne soluble platinum are present in precious metals refineries (Section 11 of Chapter 3). Furthermore, recommendations (Section 14) are made on the reporting of respiratory exposure monitoring results, the type of exposure monitoring to be conducted and the tasks or occupations to be included in the monitoring programme.

2.2.1.1 Methods for assessing respiratory exposure to platinum

The methods used to assess respiratory exposure to soluble platinum are presented, in detail, in Table 2 of Chapter 3. These methods usually involves drawing air at 2 l/min through a mixed cellulose ester (MCE) filter (which is connected to an inhalable fraction particulate sampler) and subsequent chemical analysis using inductively coupled plasma-atomic emission spectroscopy (ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS) (HSE, 1996; IPA, 2016).

2.2.2 Dermal exposure

Occupational hygiene, in general, has traditionally placed more emphasis on respiratory exposure compared to dermal exposure and the skin was only viewed to be an important exposure route of pesticides, polycyclic aromatic hydrocarbons and certain solvents (Schneider *et al.*, 2000; Sartorelli, 2002; Semple, 2004). However, the importance of dermal exposure to hazardous metals such as beryllium, nickel, lead, chromium and cobalt has been demonstrated in the last decade (Hughson *et al.* 2005; Day *et al.,* 2007; Day *et al.*, 2009; Du Plessis *et al.*, 2010; Hughson *et al.* 2010; Julander *et al.*, 2010; Franken *et al.*, 2015a; Klasson *et al.*, 2017). Despite the association of occupational exposure to chloro-complexes of platinum with the consequent development of adverse skin conditions such as allergic contact dermatitis (Gad, 2005), levels of dermal exposure in occupational settings have not yet been characterised and the amount of soluble platinum present on the skin of workers has not been established.

2.2.2.1 Methods for assessing dermal exposure to metals

The methods available for the assessment of dermal exposure are quite diverse and each method has their own advantages and disadvantages. It is important that the user should be

acutely aware of the advantages and disadvantages associated with the specific method being used (Van Hemmen and Brouwer, 1995; Du Plessis *et al.*, 2008). These methods can be grouped into three categories, namely interception methods, removal methods and fluorescent tracer methods (Du Plessis *et al.*, 2008).

Interception methods use a collection medium which can collect the contaminant in a similar way to the skin. The medium is often in the form of a patch or cotton glove and is placed on the skin. Following exposure, the medium is analysed, and the results are used to estimate the concentration of the contaminant that would have deposited onto the skin (Van Hemmen and Brouwer, 1995). Interception methods have been used to measure dermal exposure to pesticides, drilling fluids, heavy fuel oil, crude oil and polycyclic aromatic hydrocarbons (Du Plessis *et al.*, 2008; Christopher *et al.*, 2011; Garrigou *et al.*, 2011; Galea *et al.*, 2014).

Removal methods use wiping, washing, tape stripping or suction procedures to remove contaminants from the surface of the skin. The amount of contaminant which is removed represents the actual amount of contaminant present on the skin and available for absorption. It does not, however, account for the amount of the contaminant which has already been absorbed into the skin. Some skin wipe sampling methods have been validated and used to measure dermal exposure to pesticides, polycyclic aromatic hydrocarbons and metals (Van Hemmen and Brouwer, 1995; Du Plessis *et al.*, 2008; Du Plessis *et al.*, 2010; Julander *et al.*, 2010; Linde *et al.*, 2012; Du Plessis *et al.*, 2013).

Fluorescent tracer methods involve adding a fluorescent tracer to the production process containing the contaminant and visualising the dermal exposure afterwards. Following exposure to the contaminant and deposition thereof (along with the fluorescent tracer) onto the skin, the contamination can be qualitatively visualised using a long-wave ultraviolet light and recorded with a camera. Fluorescent tracer methods have been used to visualise exposure to pesticides and metal working fluids (Van Hemmen and Brouwer, 1995; Du Plessis *et al.*, 2008; ISO, 2011). Since a removal method using wipes is used during this study, later discussion of methodologies is focussed on wipe methodologies only.

2.2.2.2 Skin wipe sampling

Skin wipe sampling can be defined as the removal of a contaminant from the skin contaminant layer by applying an external force, equal to or larger than the adhesive force between the contaminant and the defined surface area (Brouwer *et al.,* 2000; ISO, 2011). This method has proven to be an effective tool for the measurement of dermal exposure to metals (Lidén *et al.,* 2006; Day *et al.,* 2009; Du Plessis *et al.,* 2010; Hughson *et al.,* 2010; ISO, 2011). It is best suited for substances, such as metals, with a low volatility, and which can be present on the skin

for a significant period of time after contamination. During the past two decades, dermal wipe sampling methods have been developed and successfully used to assess dermal exposure. Consequently, a number of publications have reported occupational dermal exposure to metals such as beryllium, lead, chromium, cobalt, and nickel in a variety of workplaces (Lidén *et al*., 2006; Day *et al*., 2009; Du Plessis *et al*., 2010; Hughson *et al*., 2010; Julander *et al.*, 2010; Du Plessis *et al*., 2013; Midander *et al.*, 2014; Kettelarij *et al.*, 2016; Klasson *et al.*, 2017). Skin wipes can vary in material, shape and size and can be used either wetted with a chemical (deionised water or diluted nitric acid), to enhance sampling efficiency, or dry (Lidén *et al*., 2006; Du Plessis *et al*., 2008). Some moistened skin wipes are commercially available (e.g. Ghostwipes™) and have successfully been used for dermal sampling of nickel compounds (Hughson *et al*., 2010; Du Plessis *et al*., 2010).

Some international health and safety organisations such as the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Association (OSHA) in the United States of America (USA) have developed wipe sampling methods for surfaces. NIOSH has published method 9102 for the collection and analysis of elements on surfaces using wipes (NIOSH, 2003) and OSHA has published method ID-125G for the collection and analysis of metal and metalloid particulates on surfaces using Ghostwipes™ (OSHA, 2002). These methods involve wiping a demarcated area with a commercially available wipe such as Ghostwipes™. The demarcated surface is wiped in an S-motion, folded, wiped for a second time, folded again and wiped for a third time. Then the wipe is stored in a hard-walled sampler container. Next, metals are extracted using nitric acid and perchloric acid, and analysed using inductively coupled argon plasma-atomic emission spectroscopy (OSHA, 2002; NIOSH, 2003).

Lidén *et al.* (2006) has developed an acid wipe sampling technique for the assessment of dermal exposure to nickel, chromium and cobalt which has been used in various occupational dermal exposure studies (Julander *et al.*, 2010; Midander *et al.*, 2014; Kettelarij *et al.*, 2016; Klasson *et al.*, 2017). This method involves wiping the demarcated area on the skin consecutively with three cellulose wipes which are moistened with 0.5 ml of 1% nitric acid. The wipes are then pooled in the same container and 23.5 ml of 1% nitric acid solution is added for extraction using ICP-MS (Lidén *et al.*, 2006).

Wipe sampling can be performed by making use of templates with a defined opening in order to sample a specific surface area of a body (Du Plessis *et al.,* 2010; Hughson *et al.,* 2010). Alternatively, it can be carried out over a specified anatomical surface area by keeping within anatomical markers (Day *et al.,* 2009; Du Plessis *et al.,* 2010). The anatomical area typically included in dermal exposure sampling strategies is the palm of the hand, while areas such as

the back of the hand, wrists, forearms, fingers, neck, face (perioral area), forehead and the chest have also been used (Lidén *et al.*, 2006; Day *et al.*, 2009; Du Plessis *et al.*, 2010; Hughson *et al.*, 2010; Julander *et al.*, 2010; Klasson *et al.*, 2017).

None of the methods described in the above sections have been validated for any of the PGMs. As with all methods used in exposure monitoring, it is extremely important to validate the sampling media that is used to remove the contaminant from the skin (Brouwer *et al.,* 2000). This is done under specific circumstances, and confirms the sampling media's capability to collect and contain the contaminant for subsequent analysis (Du Plessis *et al.,* 2008). Removal methods are validated for use by assessment of the recovery and removal efficiencies. Recovery efficiency is "the mass of compound recovered from the sampling medium divided by the total mass of compound originally deposited on the sampling medium". Samples are spiked with a known quantity of the contaminant and analysed. The results of the analysis determine whether an acceptable mass of the contaminant has been recovered from the sample. Removal efficiency is "the amount of the contaminant deposited on the skin which is actually removed by the wipe". Surfaces (usually glass plates) are spiked with a specified amount of the contaminant and wiped with the sampling media which is then analysed (OSHA, 2002; ISO 2011; Galea *et al*., 2014). According to the International Organisation for Standardisation's (ISO) Technical report *ISO/TR 14294: Workplace exposures – Measurement of dermal exposure – Principles and methods*, "efficiencies between 70% and 120% with coefficients of variation of 20% generally demonstrate the capability of an analytical laboratory to perform accurate and precise measurements" (ISO, 2011). Wipe sampling efficiency studies have reported the wipe removal efficiencies of metals other than PGMs from glass plates using Ghostwipes™. The recovery percentages for metals such as cobalt, copper, nickel and lead were all above 80% (OSHA, 2002).

2.2.2.3 General information on dermal absorption

The skin consists of three layers, the epidermis, the dermis and the hypodermis. The outermost layer of the epidermis is the non-viable stratum corneum, which consists of corneocytes that have lost their nuclei and are filled with keratin. The stratum corneum is mechanically strong and is the major barrier to permeation and chemical assault (WHO, 2006; Martini *et al*., 2014). The stratum corneum acts as the rate limiting barrier (Schneider *et al.*, 2000) and any mechanical damage to the barrier will cause an increase in the absorption of chemicals into the systemic circulation (Semple, 2004).

The dermal absorption of chemicals via the skin varies from workplace to workplace and from individual to individual. Factors that affect the amount of chemical absorbed through the skin

can be divided into chemical factors, exposure factors and skin factors (Van Hemmen and Brouwer, 1995; Semple, 2004).

The chemical factors that determine whether the chemical is capable of permeating through the skin and include characteristics of the specific chemical itself, such as its molecular weight, solubility and structure (Semple, 2004). For example, some metals such as titanium do not permeate through the skin, while other metals such as lead or cobalt are readily absorbed through the skin (Franken *et al.*, 2015a). In the case of soluble platinum, *in vitro* skin permeation studies have shown that a small mass of platinum can permeate through intact human skin (Franken *et al.*, 2014; Franken *et al.*, 2015b). During experimental animal studies, Roshchin *et al.* (1984) applied ammonium chloroplatinate to the skin of rats and found platinum in the internal organs and urine of the animals, indicating that it had been absorbed through the skin and into the systemic circulation. This led the authors to comment that, during industrial conditions, chloroplatinate compounds would probably enter workers through intact skin. As is discussed in Section 2.5 of this thesis, adverse health effects of the skin of workers have been shown to occur in precious metals refineries and autocatalyst production plants (Hunter *et al.*, 1945; Cristaudo *et al.*, 2005). Furthermore, it has been suggested that dermal exposure to soluble platinum might play a role in the development of sensitisation to soluble platinum (Maynard *et al.*, 1997). The adverse effect that the chemical has on the skin or other parts of the human body is the ultimate measure to assess the dermal risk it poses in the workplace (Schneider *et al.*, 2000). This adverse effect may occur due to the chemical permeating though the skin or through local irritation or the elicitation of allergic reactions (Semple, 2004). If the chemical can permeate through the skin and contribute to the body burden then the degree of skin permeation needs to be considered. The abovementioned literature indicates that soluble platinum has the potential to be absorbed into the systemic circulation and that dermal exposure to soluble platinum should be contenplated when assessing workplace exposure.

Exposure factors affecting skin absorption include the characteristics of the workplace such as the type and duration of the tasks performed by the workers, the use of PPE, the area of the skin which is exposed, the concentration of the chemical present as well as the washing and administrative procedures implemented in the specific workplace (Semple, 2004; Cherrie *et al.*, 2010). Exposure to chemicals in the workplace has been shown to fluctuate over time and among individual workers as a result of fluctuations in source emissions and worker behaviour (Van Hemmen and Brouwer, 1995). Occlusion resulting from the use of gloves by workers may also increase the absorption of the contaminant, if it is present on the inside of the glove. Occlusion leads to increased blood flow and sweating on the inside of the glove. Additionally there is no opportunity for the contaminant present on the inside of the glove to be removed (Cherrie *et al.*, 2010). The use of PPE, and especially gloves needs to be carefully managed

since its effectiveness is highly dependent on correct use and regular replacement. It can lead to a possible false sense of security and worker behaviour (e.g. unnecessary prolonged contact with contaminants) which might result in increased exposures (Semple, 2004; Cherrie *et al.*, 2010).

Skin or endogenous factors such as race, skin type and condition, occlusion and differences between the skin's characteristics at different anatomical areas may influence dermal absorption (WHO, 2006). In an *in vitro* permeation study that investigated the difference between the permeation of platinum through Caucasian and African skin, significantly higher permeation was reported through intact African skin compared to intact Caucasian skin. The African skin retained a significantly higher mass of platinum inside the skin (Franken *et al.*, 2015b). This information is vital to this thesis since the majority of workers who participated in this study are African. Also, the condition of the skin will impact on its ability to function as a barrier and pathological factors such as psoriasis and eczema may increase the permeability of the skin to chemicals (Sartorelli, 2002; WHO, 2006; Cherrie *et al.*, 2010).

Physical factors such as exposure to sunlight, mechanical damage or occlusion and chemical factors such as exposure to solvents or detergents may increase the permeability of the skin to hazardous chemicals (Sartorelli, 2002; WHO, 2006). All anatomical areas of the skin are not identical in terms of their thickness, hair follicle density and epidermis to dermis ratio. Consequently, the amount of the contaminant absorbed will be dependent on the specific anatomical site where exposure occurs and it is, therefore, important to investigate in what way the contaminant is distributed over various parts of the body (Van Hemmen and Brouwer, 1995; Semple, 2004).

2.2.2.4 Factors influencing dermal exposure

Compared to respiratory exposure, it is not entirely clear how dermal exposure data should be interpreted, since there are several factors influencing dermal exposure in the workplace (Schneider *et al.*, 2000). Firstly, the specific chemical is an important consideration since different chemicals pose varying risks for dermal absorption (Franken *et al.*, 2015a). Secondly, the manner of deposition on the skin of a hazardous substance may vary from workplace to workplace. Possible ways for hazardous substances to be deposited onto the skin include direct contact with the source, deposition of airborne contaminants and contact with contaminated surfaces or PPE and clothing (Schneider *et al.*, 2000). The frequency with of the occurrence skin symptoms has been shown to be dependent on the concentration of soluble platinum in solutions or in workplace air (Hunter *et al.,* 1945; Roshchin *et al.,* 1984). These findings suggest that the deposition of airborne soluble platinum onto the skin of workers is a prominent route of skin contamination. Additionally, these routes of skin contaminant deposition may interact with

each other. For example, surface contamination can become resuspended into the air by cleaning activities or contaminants can be transferred from a surface to the worker's clothes or from one anatomical area (e.g. the hands) to another (e.g. the neck) (Schneider *et al.*, 2000). Moreover, dermal exposure may also lead to exposure via ingestion by incidental contact of contaminated hands with the mouth or food (Deubner *et al.,* 2001).

Another factor which could affect the measurement of dermal exposure to soluble platinum is the possible removal of the contaminant from the skin before it has been absorbed into the skin (Schneider *et al.*, 2000). During a recent *in vitro* skin permeation study (Franken *et al.,* 2014), permeation of soluble platinum through the skin was observed after one hour of exposure and the lag time, which refers to the time it takes for the permeation of platinum through the skin to reach a steady state (McDougal and Boeniger, 2002), was 3.5 hours (Franken *et al.,* 2014). In an occupational setting such as a precious metals refinery, the soluble platinum present on the skin can potentially be removed through contact with other surfaces or clothing as well as through washing practices. This complicates the interpretation of dermal exposure measurements, since it is uncertain if the soluble platinum present on the skin will actually have time to be absorbed into the skin. As is stated by Schneider *et al.* (2000), it truly is a complex, but challenging task to assess dermal uptake quantitatively.

2.2.3 Ingestion

The effect of ingestion on the urinary platinum excretion is unclear. In a recent study investigating the contribution of the dermal and respiratory exposure routes to cobalt uptake, the authors stated that unintentional ingestion from hand-to-mouth contact should be considered as a possible route of exposure (Klasson *et al*., 2017). Gorman Ng *et al.* (2016) concluded that the time workers spent between tasks, their use of PPE, as well as personal factors such as smoking and nail biting, influenced the frequency of contact between their hands (or other objects) and their mouths (or perioral areas).

Gorman Ng *et al.* (2016) observed the behaviour of workers in several industries (including a precious metals smelter) and reported that hand-to-mouth contact took place, on average, 6.3 times per hour. Studies on occupational exposure to other metals such as lead, cadmium and arsenic have shown that inadvertent ingestion resulting from hand-to-face movements could result in substantial increases in body burden (Deubner *et al.*, 2001). The evidence for other metals suggest that the possibility of unintentional ingestion of soluble platinum exists in precious metals refineries.

Inhalation of soluble platinum is of greater importance in terms of health risks (Wiseman and Zereini, 2009) and rat studies have shown that exposure to platinum compounds by means of

the respiratory route of exposure is a more effective route of absorption compared to ingestion where < 1% of the ingested dose is absorbed (Moore *et al.,* 1975a; Moore *et al.,* 1975b). However, the presence of soluble platinum on the hands of workers could still lead to inadvertent ingestion and possible increases in platinum body burden, although this contribution is expected to be very small.

2.2.4 Biological monitoring

In Chapter 4 of this thesis, information on the biological monitoring of platinum, as well as the application thereof in precious metals refineries are presented in detail. Therefore, the biological monitoring of platinum in occupational and environmental settings will be discussed briefly in the following sections.

2.2.4.1 Background

Biological monitoring reflects the total dose of a chemical a worker is exposed to and can be used to as a tool to perform risk assessments and risk management. It reflects exposure via all possible routes of exposure and considers the possible accumulation of the chemical in the human body (Aitio *et al.,* 2006; Angerer *et al*., 2007). Once an increased risk has been identified and control measures have been implemented, biological monitoring can be used to evaluate the effectiveness of the control measures, the PPE used by workers and other work practices (Angerer *et al.,* 2007; ACGIH, 2017). In general, the decision of which biological medium to use is determined by the kinetics of the chemical in the body, the convenience of sample collection and the risk for sample contamination (Iavicoli *et al*., 2007).

Urine spot samples are often used during the biological monitoring of metals and have the advantage of being relatively simple, convenient, cheap, non-invasive and is generally accepted by workers (Iavicoli *et al.*, 2007; Wang *et al.*, 2014). The measurement of chemical concentrations (such as platinum) in urine are interpreted as direct surrogates of the external exposure level and is normally found to be linear to the exposure concentration (Aylward *et al.*, 2014). Nevertheless, concerns have been raised regarding the ability of spot urine samples to accurately reflect individual exposure over time due to the potential variability associated with urine excretion (Smolders *et al.,* 2014; Wang *et al*., 2014). Variation in external exposure is the greatest determinant of the levels of a biomarker present in the body. However, biomarker levels can vary between individuals, across days as well as within an individual and within specific days. Therefore, certain factors need to be understood in order to perform accurate biological monitoring. These factors include the characteristics of the chemical of interest, the applicable routes of exposure, the duration and frequency of exposure and the physiological characteristics of the biological matrix and the individual. In particular the biological half-life of

the chemical and the characteristics of exposure can greatly influence variations in biomarker concentrations (Aylward *et al*., 2014). Schierl *et al.* (1995) reported low intra- and inter-individual variability in the platinum concentrations of spot urine samples collected from patients who were treated with cis-platin during chemotherapy and remarked that spot urine samples can be used instead of 24 hours samples. As is discussed in the following sections, platinum in spot urine samples have been used in various occupational and environmental exposure studies as a biomarker for exposure to platinum compounds.

2.2.4.2 Biological monitoring of occupational exposure

The contribution of low-level exposure to soluble platinum in causing adverse health effects are unclear and the determination of platinum in biological fluids can aid in individual exposure assessment and risk assessment (Iavicoli *et al.*, 2007). Urine has been identified as a reliable biological matrix when performing biological monitoring of platinum exposure and has been used in numerous studies in occupational settings (Schaller *et al*., 1992; Farago *et al.,* 1998; Schierl *et al.,* 1998; Petrucci *et al.,* 2005; Cristaudo *et al.,* 2007). Cristaudo *et al*. (2007) reported platinum concentrations in workplace air and in biological samples (urine, blood and hair) of catalyst production and metal recycling workers. They observed a high correlation between platinum levels in the workplace air and platinum levels in the urine of workers (r = 0.918) and established that urine is a reliable biomarker of short term exposure to platinum. Urinary platinum excretion may be used in distinguishing between subjects who work in high exposure areas and those who work in areas with lower exposure (Petrucci *et al.,* 2004; Petrucci *et al.*, 2005). Both Farago *et al*. (1998) and Schaller *et al*. (1992) reported significantly higher urinary platinum excretion for occupationally exposed persons (such as refinery workers) compared to persons who were exposed to platinum in the environment such as motorway workers and persons from the general population. Schierl *et al.* (1998), who exposed two human volunteers with normal urinary platinum excretion to soluble platinum, reported that the urinary platinum excretion increased sharply in the first urine samples following the cessation of exposure. Even 4000 hours after exposure had ceased the urinary platinum excretion was still above the baseline concentrations. However, the urinary platinum excretion was within the range observed in non-occupationally exposed persons. Even though the urinary platinum excretion concentration was found to be a reliable biomarker for occupational exposure, platinum in biological samples was not correlated with hypersensitivity (Cristaudo *et al.,* 2007).

The urinary platinum excretion of workers in hospitals (preparation of antineoplastic drugs) and dental technicians (treatment of dental alloys with platinum) have also been reported (Begerow *et al.,* 1999; Kopp *et al.,* 2013). However these concentrations did not reach the concentrations measured in refineries and automotive catalyst plants (Kiilunen *et al*., 2015).

The findings from previous occupational biological monitoring studies are extensively discussed in Chapter 4 of this thesis.

2.3 Environmental exposure

With the increased use of PGM containing automotive catalysts to reduce the emission of NO_x, CO and various hydrocarbons from automobiles, the presence of PGMs in the ambient air have been investigated (Wiseman, 2015) and is deliberated briefly in the following section.

2.3.1 Environmental exposure to airborne platinum

Prior to the introduction of automotive exhaust catalysts, the concentration of platinum in ambient air was reported to be below the limit of detection of 0.05 pg/m^3 (Ravindra *et al.*, 2004). Since then the concentration of platinum in ambient particulate matter has increased significantly (Bencs *et al.*, 2011; Zereini *et al.*, 2012; Wiseman, 2015). Zereini *et al.* (2012) reported a mean platinum concentration of 12.4 pg /m^3 (range = 1.2 to 80.9 pg/m^3) in PM_{10} samples collected in Frankfurt, Germany between 2008 and 2010. Chellam and Bozlaker (2015) reported an average platinum concentration of 15.1 pg/m^3 in ambient PM_{10} samples collected in Houston, Texas and an average platinum concentration of 61.1 pg/m^3 in PM_{10} samples collected in a high traffic tunnel. Reviews by Wiseman and Zereini, (2009) and Bencs *et al.* (2011) both contain summaries of the findings for studies reporting concentrations of platinum in airborne matter. In general, the concentrations of platinum in airborne particulate matter vary according to location and it is strongly related to traffic density and the strength of the local emission sources (Bencs *et al.*, 2011; Zereini *et al.*, 2011). Subsequently, airborne particulate matter (PM_{10}) in urban areas has been shown to contain significantly higher concentrations of platinum compared to particulate matter (PM_{10}) in rural areas (Zereini *et al.*, 2012). Some occupations, such as police officers and tram drivers, are also exposed to platinum originating from environmental sources such as roadside dust. Iavicoli *et al.* (2008) reported the mean exposure of tram drivers to platinum in roadside dust in Rome to be 14.1 pg/m^3 for PM_{10}.

Although platinum from automotive exhaust catalysts is primarily emitted in a metallic state which is associated with low allergic reactivity (Di Gioacchino *et al.*, 2004; Cristaudo *et al.*, 2005), it has been suggested that the health risk of these emissions are greater than previously suspected (Wiseman, 2015). The reason being that either platinum may possibly be mobilised and solubilised by compounds present in the environment or that it may be transformed into more toxic substances following uptake (Wiseman and Zereini, 2009). Recent bio-accessibility studies on post-emission platinum in the environment have indicated that there is a concern associated with low dose environmental exposure (Wiseman, 2015). Puls *et al.* (2012) investigated the bio-accessibility of platinum from urban aerosol particulates and demonstrated

that 26% of platinum PM_{10} airborne particulate matter collected in Vienna was soluble in synthetic gastric juice. Furthermore, it has been suggested that platinum present in the respiratory tract may form chloro-platinum complexes in the presence of chloride in the lung fluids, which could lead to toxic effects (Colombo *et al.*, 2008). However, the potential of environmental exposure to platinum causing respiratory sensitisation is unclear. Although it has been suggested that environmental exposure to platinum may elicit effects on a subclinical level (Wiseman, 2015), medical surveillance studies conducted in occupational settings have not reported respiratory sensitisation to take place in control subjects outside of the workplace (Merget *et al.*, 2000; Cristaudo *et al.*, 2005). After investigating occupational hypersensitivity to soluble platinum in an automotive catalyst production plant, Cristaudo *et al.* (2005) reported that none of the non-exposed persons or workers from areas outside the production area were sensitised to soluble platinum. Additionally, exposure to concentrations of soluble platinum in the range found in the environment did not increase the frequency of reaction to soluble platinum in persons with dermatitis and or urticaria (Santucci *et al.*, 2000).

For further information on the effect of environmental exposure to platinum group metals on human health, the reader is referred to review articles by Bencs *et al.* (2011) and Wiseman (2015).

2.3.2 Biological monitoring of environmental exposure

Numerous studies have reported urinary platinum excretion resulting from environmental exposure to be in the range of 0.001-20 ng/l (Schaller *et al.*, 1992; Schierl *et al*., 1998; Petrucci *et al*., 2005; Cristaudo *et al*., 2007; Iavicoli *et al*., 2007). Recently, the *Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2017* reported biological monitoring data on 308 chemicals (including platinum) as measured among the general USA population between 1999 and 2010. For urinary platinum from 2009 to 2010, the 95th percentile of the total population (six years and older) was 0.016 µg/l (range = 0.009-0.049 µg/l; n = 2847); the 95th percentile of the 20 years and older population was 0.017 µg/l (range = 0.009-0.049 µg/l; n = 2018). For creatinine corrected urinary platinum in 2009-2010, the 95th percentile of the total population was 0.033 µg/g creatinine (range = 0.026-0.046 µg/g creatinine; n = 2847); the 95th percentile of the 20 years and older population was 0.035 µg/g creatinine (range = 0.024-0.050 µg/g creatinine; n = 2018). The limit of detection for the measurements was 0.009 µg/l (CDC, 2017).

Urinary platinum excretion of persons exposed to platinum in road dust are dependent on the location of the exposure and whether the area has high or low traffic densities (Farago *et al*., 1998). In a study conducted in Rome, the urinary platinum excretion of police officers, who were occupationally exposed to platinum in road dust, and office workers were compared. No

statistically significant differences were observed between the urinary platinum excretion of police offices (range = 0.28-13.67 ng/l) and that of the office workers (range = 0.20-15.29 ng/l) (Iavicoli *et al*., 2004). Similarly, the average urinary platinum excretion of tram drivers in Vienna and Budapest were reported to be 12.6 and 22.8 ng/g creatinine respectively (Óvári *et al*., 2007).

Platinum-containing dental or medical devices have been shown to increase urinary platinum excretion and is one of the main sources of platinum exposure in non-occupationally exposed persons (Schierl *et al*., 2001; Herr *et al*., 2003) and low concentrations of platinum have also been identified to be present in food such as white bread (0.257 µg/kg) and full-cream cow's milk (0.083 µg/kg) (Frazzoli *et al*., 2006). Age has also been shown to have a minute influence on the internal platinum exposure of the environmentally exposed persons (Herr *et al.*, 2003). Therefore, in addition to environmental exposure to platinum from road dust (Iavicoli *et al*., 2004) increases in urinary platinum excretion in general population can be caused by platinum in dental fillings and in food (Frazzoli *et al*., 2006; Herr *et al.*, 2003; Schierl *et al*., 2001).

2.4 Platinum toxicology

In order to accurately perform biological monitoring, it is important to understand the absorption, distribution, metabolism and elimination of a chemical in the body as it has a substantial effect on the accuracy of the measurements (Aylward *et al.*, 2014). The following sections contain a summary of the absorption, distribution and elimination of platinum as reported in animal (Section 2.4.1.) and human studies (Section 2.4.2.).

2.4.1 Animal studies

2.4.1.1 Absorption

Comparisons between studies where rats were exposed to various forms of platinum by means of inhalation and ingestion exposure indicated that the inhalation route of exposure is a more effective route of absorption compared to ingestion (Moore *et al.,* 1975a; Moore *et al.,* 1975c). Whole body retention of platinum was measured in rats following single dose exposure via the oral route. Results indicated that less than 1% of the initial dose was absorbed by the gastrointestinal tract (Moore *et al.,* 1975b). Artelt *et al.* (1999) exposed rats to an oral dose of oxo(oxoalumanyloxy)alumane platinum ($PtAl_2O_3$) and established that approximately 0.11% of the platinum dose was absorbed. Following single dose oral, intravenous and inhalation administrations of platinum tetrachloride ($PtCl_4$) to rats, Moore *et al.* (1975b) observed the lowest retention taking place following oral exposure and the highest via the intravenous pathway. Therefore, evidence from animal studies suggests that absorption of platinum from the

gastrointestinal tract following an oral dose is very low (<1%) (Moore *et al.,* 1975b; Moore *et al.,* 1975c; Reichlmayr-Lais *et al.,* 1992; Artelt *et al.,* 1999).

Following exposure of rats to various soluble and insoluble forms of platinum, Moore *et al.* (1975a) reported that the platinum was either deposited in the lungs, absorbed and distributed to other organs or cleared from the lung by mucociliary clearance to the gastrointestinal tract. Moore *et al.* (1975c) exposed rats to platinum via inhalation and although most of the platinum was excreted in the faeces, the small amount of platinum excreted in the urine indicated that a small amount of platinum was absorbed. Therefore, the platinum in the urine was representative of the amount of platinum absorbed into the circulation following exposure.

Roshchin *et al.* (1984) applied chloroplatinates to the skin of guinea pigs and reported that platinum was found in all the internal organs, the urine and the blood following the experiment. The authors indicated that soluble platinum compounds could be absorbed via the skin and that dermal exposure to these compounds in occupational settings could contribute to the total platinum body burden. However, this statement should be interpreted cautiously and the difference between the skin anatomy of humans and guinea pigs should be considered.

2.4.1.2 Distribution

In the blood plasma of rats, 90% of bioavailable platinum is bound to proteins while the remaining platinum is present as low molecular weight compounds such as ionic complexes (Artelt *et al.,* 1999). Following absorption into the circulation via different exposure routes, rat studies have shown distribution of platinum to various organs, including the kidneys (highest concentration), liver, spleen and bones (Holbrook *et al.,* 1975; Moore *et al.,* 1975a; Moore *et al.,* 1975b; Moore *et al.,* 1975c; Reichlmayr-Lais *et al.,* 1992). In a dose-response study, growing rats were fed a diet containing various concentrations of platinum(II)chloride ($PtCl_2$) and $PtCl_4$. Retention of platinum was seen in almost all types of tissue with the highest retention in the kidneys, which increased with higher doses. The authors reported increased serum creatinine levels (which is indicative of reduced kidney function) and retention in the kidneys for $PtCl_4$ (slightly soluble) compared to $PtCl_2$ (insoluble) (Reichlmayr-Lais *et al.,* 1992). The general mechanism of the toxic effects which platinum compounds elicit in the kidney is based on its interaction with the sulfhydryl groups of various proteins and enzymes (Roshchin *et al.,* 1984). The retention pattern of platinum in the rat organs suggested that complex platinum compounds may be too large to cross the blood brain barrier (Moore *et al.,* 1975b; Moore *et al.,* 1975c).

2.4.1.3 Elimination

Platinum which is ingested and passed through the gastrointestinal tract unabsorbed or inhaled platinum which is removed by mucociliary transport and swallowed is excreted in the faeces of rats whereas intravenously administered platinum is excreted in the faeces and urine (Moore *et al*., 1975b; Moore *et al*., 1975c). Retention curves from Moore *et al*. (1975c) showed platinum clearance from rats exposed via inhalation taking place in two phases. Initially, there is a rapid clearance of platinum from the body which is followed by a slower clearance phase over the remainder of the post-exposure period. These studies show that the initial high excretion of platinum following exposure via inhalation and the oral routes can be attributed to platinum being removed by mucociliary and alveolar clearance and passing through the gastrointestinal tract unabsorbed. The slower second phase then represents the absorbed platinum being excreted in the urine and the faeces. Roshchin *et al.* (1984) reported that ammonium chloroplatinate, which has high water solubility, is mainly eliminated in the urine.

2.4.2 Human studies

2.4.2.1 Absorption

Inhalation of platinum compounds poses a greater risk to health compared to ingestion (Wiseman and Zereini, 2009) and exposure via inhalation has been shown to cause a 15 to 1000-fold increase in urinary platinum excretion approximately 10 hours after exposure (Schierl *et al.,* 1998). Although very low concentrations of platinum have been identified to be present in food (Frazzoli *et al.,* 2006), the oral route of exposure is not significant because absorption of platinum by the gastrointestinal system is very poor (Gad, 2005). Using data from previous studies the United States (U.S.) Department of Health and Human Services has calculated a permitted daily exposure level of 108 µg/day for the oral route and 1.4 µg/day for inhalation (U.S. Department of Health and Human Services, 2015).

Very low amounts of platinum (from a solution of potassium tetrachloroplatinate) have been reported to permeate through intact human skin during *in vitro* experiments (Franken *et al.,* 2014; Franken *et al.,* 2015b). Both Franken *et al.* (2014) and Franken *et al.* (2015b) reported that a substantial mass of platinum was retained within the skin following the *in vitro* experiments and suggested that this could result in the release of platinum into the circulation after exposure had ended.

2.4.2.2 Distribution

Following the ingestion of platinum-containing water, platinum was found in the kidneys and liver (Gad, 2005). Duffield *et al.* (1976) determined the human tissue platinum burdens of

autopsied individuals prior to the widespread use of automotive catalytic converters and observed detectable concentrations of platinum in 45 of the 97 autopsied individuals. The concentrations varied greatly (<1 to 1200 ng/g wet tissue) and the highest concentrations of platinum were detected in subcutaneous fat, followed by the kidneys, pancreas and liver. Benes *et al.* (2000) reported platinum concentrations in the kidneys, liver and bones of autopsied individuals and also reported a high degree of variation (kidney, 2.5 – 750 µg/kg wet weight; liver, 2 – 3920 µg/kg wet weight; and bone, 10 – 230 µg/kg wet weight).

Schierl *et al.* (1998) reported that employees who were no longer exposed to platinum for two to six years, still excreted 25 times more platinum than unexposed people from a control group. This indicated a long term platinum reservoir might form in the body from where platinum may become systemically available and excreted via the urine.

2.4.2.3 Elimination

Ingested platinum which has not been absorbed or inhaled platinum which has been removed by mucociliary transport is excreted in the faeces (Gad, 2005). Schierl *et al.* (1998) reported the urinary platinum excretion of two volunteers after they had been exposed to ammonium hexachloroplatinate dust for four hours. The volunteers were without previous occupational exposure and showed a 15 to 100-fold increase in urinary platinum excretion in the first urine samples following exposure. Their urinary platinum excretion reached the maximum approximately ten hours after exposure had ceased. Their urinary platinum excretion followed a biphasic exponential decay pattern and the authors reported a first half-life of approximately 50 hours [36-66 hours, 95% confidence interval (CI)] and a second half-life of approximately 24 days (18-33 days, 95% CI). The volunteers' urinary platinum excretion was still above the concentrations prior to exposure up to 167 days after exposure (Schierl *et al.*, 1998).

During the study by Schierl *et al.* (1998), the urinary platinum excretion of workers who were exposed to low concentrations of airborne soluble platinum dust, was closer to that of the unexposed control group than that of the high exposure group. This showed that urinary platinum excretion is dependent on exposure. The use of urinary platinum excretion as a biomarker to evaluate the exposure of individual workers to platinum was mentioned in Section 2.2.4.2 of this chapter and is considered to be the best approach since it allows for environmental and occupational levels to be easily distinguishable (Schierl *et al*., 1998; Cristaudo *et al*., 2007; Iavicoli *et al.,* 2007).

2.5 Platinum toxicity and health effects

Even though platinum is a vital chemical in modern life, the mining, refining and processing thereof hold significant occupational health risks. Of these risks, soluble platinum sensitisation is the greatest (Bullock, 2010). The toxicity of platinum is limited to certain complex halide salts as well as chemotherapeutic drugs such as cis-platin, carboplatin and their analogues (WHO, 2000). The discussion of platinum exposure and toxicity in this thesis focuses on complex halide platinum salts and, therefore, the toxic effects of chemotherapeutic drugs will not be discussed.

Metal speciation is very significant in determining the toxicity of platinum compounds (Linnett and Hughes, 1999; Ravindra *et al.,* 2004). The toxicity of metallic platinum is low (Kiilunen *et al.,* 2015), whereas platinum complexes containing reactive halide ligands frequently cause allergic reactions of the airways and skin (Cleare *et al.,* 1976; Roshchin *et al.,* 1984; WHO, 2000). The number of chloro-groups in the complex determines the degree of allergenicity which the compound elicits (Cleare *et al.,* 1976). Additionally not all chloride containing compounds provoke allergic reactions. For example, it has been reported that tetraammine platinum dichloride is not allergenic under normal industrial conditions (Linnett and Hughes, 1999). In rats, water soluble platinum compounds such as chloride containing complexes have been shown to be more toxic than their insoluble counterparts (Holbrook *et al.,* 1975; Roshchin *et al.,* 1984).

According to Cleare *et al.* (1976) the following sequence applies when investigating the degree of allergenicity of soluble platinum compounds: $(NH_4)_2[PtCl_6] \approx (NH_4)_2[PtCl_4] > Cs_2[Pt(NO_2)Cl_3] > Cs_2[Pt(NO_2)_2Cl_2] > Cs_2[Pt(NO_2)_3Cl] > K_2[Pt(NO_2)_4]$ (inactive). Di Gioacchino *et al.* (2004) also investigated the *in vitro* immune effects of various occupationally significant platinum compounds and ranked their immune activity in the following order: $(NH_4)_2[PtCl_6] > (NH_4)_2[PtCl_4] > Na_2Pt(IV)I_6 >$ Cis Pt(II) $> PtCl_4 > PtCl_2$

Boscolo *et al.* (2004) reported that ammonium hexachloroplatinate and ammonium hexachloropalladate showed increased immune activity compared to ammonium tetrachloroplatinate and ammonium tetrachloropalladate respectively, confirming the findings of Cleare *et al.* (1976) who stated that allergenicity increases as the number of chloro-groups in the complex increases. The ranking of ammonium hexachloroplatinate as the platinum compound with the highest immune activity by Di Gioacchino *et al.* (2004) and Boscolo *et al.* (2004) is of significant importance to this thesis since platinum is precipitated in the form of ammonium hexachloroplatinate in the precious metals refineries used in this study.

One case of attempted suicide has been reported where 10 ml of photographic toning solution containing 600 mg of potassium tetrachloroplatinate was ingested. The toxic effects which

followed included acute oliguric renal failure, metabolic acidosis, muscle cramps gastroenteritis and fever. The symptoms of poisoning were resolved after six days of supportive medical management. A spot urine sample collected from the patient showed a urinary platinum excretion of 4200 µg Pt/l (Woolf and Ebert, 1991; Kiilunen *et al.,* 2015).

Occupational exposure to platinum compounds can induce diseases of the respiratory passages (rhinitis, pharyngitis, tracheitis, asthmoidal bronchitis, bronchial asthma) and skin (contact dermatitis in the form of eczematous patches) as well as diseases of the eyes (allergic conjunctivitis) (Roshchin *et al.,* 1984; Gad, 2005). Table 1 in Chapter 3 of this thesis summarises the adverse respiratory and dermal conditions and symptoms associated with occupational exposure to PGMs and shows that respiratory sensitisation and the resulting asthma symptoms are the main adverse effects of PGMs in occupational settings. Since sensitisation to soluble platinum is the major adverse health effect associated with occupational exposure to platinum, it will be discussed in detail in the following section.

2.5.1 Sensitisation

Hnizdo *et al.* (2001) reported the findings of the Surveillance of Work-related and Occupational Respiratory Diseases in South Africa (SORDSA) which were conducted between 1996 and 1998. SORDSA identified newly diagnosed cases of occupational respiratory diseases by means of voluntary reporting by occupational health professionals and showed that platinum salts were the third most frequent cause of occupational asthma in South Africa (12.3% of occupational asthma cases), after latex (24.1%) and isocyanates (19.5%) (Hnizdo *et al.,* 2001). This was the most recent statistics available on the causes of occupational asthma in South Africa.

2.5.1.1 Mechanism of sensitisation

Soluble platinum compounds elicit a type I hypersensitivity reaction which is mediated by Immunoglobulin (Ig) E (Gad, 2005; Kaplan *et al.*, 2013; Heederik *et al.,* 2016). The mechanism of antibody production during hypersensitivity is dependent on the genetics of the individual, the characteristics of the antigen as well as environmental factors (Kaplan *et al.*, 2013). A wide variety of compounds causes respiratory allergic reactions in occupational settings. These compounds are classified as high molecular weight compounds and low molecular weight compounds. High molecular weight compounds, such as proteins found in wheat, can directly induce IgE-mediated allergic responses while low molecular weight compounds, such as soluble platinum need to bind to proteins in the body before inducing IgE-mediated allergic responses (Rijnkels *et al.,* 2008). Generally, small molecular allergenic substances such as soluble platinum compounds act as haptens. These haptens can only become fully allergenic once they

combine with large molecular carrier substances such as proteins. These hapten-carrier complexes then stimulate antibody production and elicit allergic reactions (Cleare *et al.,* 1976). Following initial exposure to the allergen via the respiratory tract, skin or gastrointestinal tract, the allergen (or hapten) binds to a carrier protein to form the antigen (hapten-protein complex) (Kaplan *et al.*, 2013). Platinum has the distinct ability to form a complete antigen by forming complexes with the donor groups of amino acids in proteins (Cristaudo *et al.,* 2005). Once the complete antigen is formed, it activates the appropriate B cells. The B cells then start dividing and differentiate into plasma cells which secrete IgE antibodies (Martini *et al.,* 2014). Next, IgE antibodies can either bind to local mast cells or enter the circulation where they can bind to circulating mast cells or mast cells of distant tissues. After an individual has been sensitised, re-exposure to minute amounts of the allergen result in the antigen binding to the IgE on the mast cells which causes immediate degranulation of the mast cells and the release of cytokines, histamines and other mediators (Martini *et al.,* 2014). These mediators stimulate vasodilatation, bronchial constriction and inflammation which lead to the clinical symptoms that are typical of platinum hypersensitivity, namely asthma, rhinitis, conjunctivitis and urticarial skin reactions (Kaplan *et al.*, 2013).

The IgE antibody is an important requirement for the development of respiratory sensitisation to chemical allergens and a strong association exists between clinical allergic symptoms caused by platinum salts and IgE production (Kimber and Dearman, 2002). Ban *et al.* (2010) challenged sensitised mice to platinum salts three, four and five times and observed a significant increase in IgE production with the highest levels being observed in the mice that experienced five challenges. The authors attributed the increased IgE production to local production of T-helper 2 cytokines and in particular, Interleukin (IL)-4 (Ban *et al.*, 2010). Increases in total IgE levels have also been associated with workers who had been sensitised to soluble platinum (Murdoch *et al*., 1986; Baker *et al.*, 1990; Bolm-Audorff *et al.*, 1992; Merget *et al.,* 2000; Merget *et al.,* 2017). Murdoch *et al*. (1986) reported that total IgE levels were increased in 63% (24 out of 38) of cases where South African platinum refinery workers had positive platinum salt skin prick tests compared to only 16% (43 out of 268) in workers who had negative platinum salt skin prick results. Bolm-Audorff *et al.* (1992) reported increased total IgE and platinum specific IgE levels in workers who experienced work-related symptoms of respiratory allergy in a refinery compared to non-symptomatic workers. Merget *et al.* (2017) performed follow-up medical examinations years after workers had been removed from exposure areas and showed a reduction in total IgE levels, indicating a decrease in antibody concentrations resulting from a cessation of exposure. The increase of IgE levels following exposure and the subsequent reduction in IgE levels following the cessation of exposure strengthens the notion that the allergenicity of soluble platinum is mediated by IgE.

2.5.1.2 Route of exposure and sensitisation

Inhalation is the most important exposure route for sensitisation of the respiratory tract in occupational settings. However, it is possible that respiratory sensitisation is not caused solely by inhalation exposure. For example, the topical application of certain respiratory allergens on experimental animals may result in respiratory sensitisation (Kimber and Dearman, 2002). Dearman *et al.* (1998) reported that topical application of three types of platinum salts on mice elicited similar immune responses (elaboration of IL-4 and IL-10) as observed following repeated topical exposure of trimellitic anhydride, a known respiratory allergen. It is, therefore, plausible that dermal exposure to soluble platinum might play a role in the development of respiratory sensitisation. After measuring airborne concentrations of soluble platinum in various platinum industries, Maynard *et al.* (1997) reported that sensitisation occurred in work areas where airborne soluble platinum concentrations were much lower than the occupational exposure limit (OEL). They suggested that sensitisation might occur via the inhalation as well as the dermal exposure routes. The exact circumstances that cause soluble platinum sensitisation are not known (Bullock, 2010). Additionally uncertainty still exists whether respiratory sensitisation to soluble platinum might occur because of respiratory exposure alone or whether it is caused by a combination of both respiratory and dermal exposure in occupational settings (Heederik *et al.*, 2016).

2.5.1.3 Sensitisation in occupational settings

The majority of information regarding the adverse health effects of platinum compounds has been collected from industrial settings, such as precious metals refineries, where workers handle complex platinum compounds (WHO, 2000; EC SCOEL, 2011). Platinum salts have been demonstrated to be important allergens in the precious metals refining and automotive catalyst production industries with clinical symptoms observed in the respiratory system and the skin of workers (Hunter *et al.,* 1945; Cristaudo *et al.,* 2005; Heederik et al., 2016).

The toxicity of platinum in an occupational setting was first described in 1911 by Karasek and Karasek (1911) who reported asthma-like adverse health effects suffered by photography studio workers who handled paper which contained potassium chloroplatinate. These adverse health effects included substantial throat, nasal and bronchial irritation, violent sneezing and coughing, and irritation of the skin which led to cracking, bleeding and severe pain. The respiratory impairment was so extensive that some workers were totally unable to work with the chloroplatinate-containing paper (Karasek and Karasek, 1911; Hunter *et al.,* 1945). In 1945, Hunter *et al.* (1945) reported that precious metals refineries workers who handled complex platinum salts experienced a condition referred to as platinosis, which consisted of rhinitis, sneezing, chest tightness, shortness of breath, cyanosis, wheezing, coughing, and watering of

the eyes as well as skin symptoms such as dermatitis and eczema. Platinosis is commonly referred to as platinum salt sensitivity or soluble platinum sensitisation (Kiilunen *et al.*, 2015) and was observed in 52 out of 91 men who were exposed to soluble platinum dusts or sprays in four British refineries (Hunter *et al.,* 1945). Thirteen of the 91 men also experienced scaly erythematous dermatitis and some urticarial rash. Work-related symptoms have been reported to occur more frequently in workers who experience high exposure to soluble platinum compared to those who experience moderate to low exposure (Bolm-Audorff *et al.*, 1992; Merget *et al.*, 2000). Respiratory symptoms usually subside a few hours after the cessation of exposure (Kiilunen *et al.*, 2015). Heederik *et al.* (2016) conducted a retrospective cohort study using routinely collected medical surveillance and exposure data from five precious metals refineries. The authors reported a clear exposure-response relationship between occupational exposure to soluble platinum and sensitisation. This relationship was more prominent for exposure in recent years before sensitisation had occurred compared to exposure further back in the past.

In 2010, it was estimated that of the 4000 workers who are exposed to chloroplatinates worldwide, approximately 1% are sensitised annually (Bullock, 2010). A study by Linnett and Hughes (1999), which was conducted in a PGM refinery, an automotive catalyst production plant and a tetraammine platinum dichloride laboratory, estimated that workers who constantly work with chemical processes where they are exposed to chloroplatinates have a 51% cumulative chance of becoming sensitised after 5 years. The latency period between the start of exposure and the development of symptoms can differ between individuals because of certain genetic factors and the time needed for the B cells to be stimulated, divide and proliferate into plasma cells that are capable of releasing immunologic mediators as described in Section 2.5.1.1 (Martini *et al.,* 2014). Bolm-Audorff *et al.* (1992) observed an average latency period of 4.8 years (range: 1 – 13 years) in 15 workers who were sensitised to soluble platinum. In two other case studies, refinery workers developed asthma-like symptoms after one and six years, respectively (LeRoy, 1975).

2.5.1.4 Management and removal of sensitised workers

The primary approach to the management of dermal and respiratory symptoms caused by exposure to soluble platinum is to remove the worker from possible exposure areas, after which the symptoms should abate (LeRoy, 1975; Gad, 2005; Bullock, 2010). However, Merget *et al.* (2017) recently revealed limitations to this approach. They conducted second examinations several years (median of 67 months) after workers were first diagnosed with soluble platinum sensitisation. They reported that although there were improvements, 77% of subjects still suffered from asthma. Although asthmatic symptoms did not totally subside with time,

symptoms such as rhinitis, conjunctivitis and contact urticaria had an improved prognosis. The authors subsequently suggested that workers should be removed from exposure areas immediately after positive skin prick tests, irrespective of whether they show symptoms or not. Brooks *et al.* (1990) also reported that asthmatic symptoms and airway hyperresponsiveness persisted for years following removal from soluble platinum exposure. The authors attributed this persistence to delays in the removal of workers from exposure areas after sensitisation had been identified. Niezborala and Garnier (1996) made recommendations aimed at reducing the risk of workers becoming sensitised to soluble platinum. These recommendations included that workers should not come into direct contact with soluble platinum in solid or liquid form; that workers should be encouraged to stop tobacco smoking; that workers with positive skin prick tests without symptoms should be removed from exposure and that workers with positive sensitisation diagnoses should be advised to leave the refinery. More recently, a paper by Rijnkels *et al.* (2008) summarised advice from the Health Council of the Netherlands with regard to the development of work-related airway allergies. The authors emphasised the importance of pre-employment as well as periodic screening in order to promote timely intervention and early identification of sensitised workers.

2.5.1.5 Risk factors for the development of soluble platinum sensitisation

As is discussed in detail in Chapter 3 of this thesis, the intensity of exposure to soluble platinum is the greatest risk factor for soluble platinum sensitisation (Calverley *et al.*, 1995; Merget *et al.*, 2000; Heederik *et al.*, 2016). Additionally smoking and atopy has also been identified as aggravating risk factors (Heederik *et al.*, 2016).

Smoking is a substantial risk factor for the development of soluble platinum sensitisation and during a study in a South African precious metals refinery, the risk of sensitisation was eight times greater for smokers, compared to non-smokers (Calverley *et al.*, 1995). Numerous other studies performed in occupational settings have also identified smoking as a risk factor for the development of sensitisation (Venables *et al.*, 1989; Baker *et al.*, 1990; Calverley *et al.*, 1995; Niezborala and Garnier, 1996; Merget *et al.*, 2000; Heederik *et al.*, 2016).

There have been contrasting findings regarding the role of atopy in the development of sensitisation (Cristaudo *et al.*, 2005). Niezborala and Garnier, (1996) reported that atopy was not a predictor of soluble platinum sensitisation and that the exclusion of atopic workers form working in a precious metals refinery did not result in a lower incidence of sensitisation. Other studies have also shown that atopic workers do not have an increased risk to be sensitised (Baker *et al.*, 1990; Bolm-Audorff *et al.*, 1992). However, some studies have reported an association between atopy and soluble platinum sensitisation (Cristaudo *et al.*, 2005; Heederik

et al., 2016) and in light of this contradiction, Merget *et al.* (2017) has described atopy as, at best, a modest predictor of soluble platinum sensitisation.

Roberts (1951) reported factors which predispose a person to become sensitive to complex platinum salts. These factors include strong family histories of hives, hay fever, asthma, contact dermatitis and previous allergies Additionally, individuals with blond hair, blue eyes, a sensitive skin as well as those prone to skin blemishes, moles, acne, sebaceous cysts and other lesions are more prone to hypersensitivity reactions (Roberts, 1951; LeRoy, 1975).

2.6 Legislative aspects of platinum exposure

The legislation applicable to occupational health and safety in South Africa is the *Occupational Health and Safety Act No. 85 of 1993 and Regulations* which is applicable to general industry (DOL, 2017) and the *Mine Health and Safety Act No.29 of 1996 and Regulations* which is applicable to the mining industry (DMR, 2017). In Section 2.6.1 to 2.6.5, the legislative aspects applicable to occupational exposure to platinum compounds is elucidated.

2.6.1 Respiratory occupational exposure limits

The South African occupational exposure limit-recommended limit (OEL-RL) for respiratory exposure to soluble platinum is set at 2 µg/m^3 (DMR, 2017; DOL, 2017). This is the same exposure limit which is set by other countries or organisations such as the American Conference of Governmental Industrial Hygienists (ACGIH) (ACGIH, 2017) and the OSHA in the USA and the Health and Safety Executive (HSE) in the United Kingdom (UK) (HSE, 2011; ACGIH, 2017; OSHA, 2017). The threshold limit value-time weighted average (TLV®-TWA) of 2 µg/m^3 for soluble platinum salts (measured as platinum) was established back in 1970 by the ACGIH and is currently still in use (ACGIH, 2017). As is discussed in detail in Section 10 of Chapter 3 of this thesis, there has been some controversy over the effectiveness of this limit to protect workers against sensitisation and the lowering of the limit for soluble platinum to as low as 5 ng/m^3 has been proposed (DECOS, 2008; Bullock, 2010). Setting an OEL for an allergenic substance is challenging since the exposure level at which no sensitisation occurs may be so low that various economical and practical reasons makes it almost impossible to implement. (Rijnkels *et al.*, 2008). Studies such as Bolm-Audorff *et al.* (1992) and Maynard *et al.* (1997) have reported cases of respiratory sensitisation to soluble platinum in workplaces where the exposure did not exceed the OEL of 2 µg/m^3 and highlighted the possibility that sensitisation might be occurring at exposure concentrations well below the OEL. These and other studies have emphasised the inability of the OEL of 2 µg/m^3 to protect workers against the allergic airway diseases (Roshchin *et al.*, 1984; Bolm-Audorff *et al.,* 1992; Maynard *et al.*, 1997; Merget

et al., 2000; DECOS, 2008). These studies as well as the legislative requirements of various countries and organisations are further elaborated on in Chapter 3.

2.6.2 The sensitiser notation

The sensitiser notation refers to the potential of a chemical to induce respiratory and/or skin sensitisation (as is discussed in Section 2.5.1.) and is based on confirmed human or animal epidemiological data (ACGIH, 2017). Once sensitised, subsequent minute exposure to the substance at concentrations below the OEL, may cause intense reactions, which can prove to be life threatening (ACGIH, 2007; Martini *et al.*, 2014). For example, respiratory sensitisation reactions have been observed in sensitised workers who were exposed to airborne soluble platinum concentration of 0.05 µg/m^3, which is 40 times lower than the OEL (Di Gioacchino *et al.*, 2004). Therefore, the sensitiser notation indicates to the occupational hygienist that exposure to the classified substances should be prevented or be kept as low as reasonably practicable and should be accompanied by appropriate health surveillance (HSE, 2011).

As is discussed in Section 10 of Chapter 3 of this thesis, some countries or organisations have classified substances as either respiratory or dermal sensitisers, or as both. In the South African Hazardous Chemical Substances Regulations, soluble platinum has been classified as a respiratory sensitiser which is indicative of its capability to cause respiratory sensitisation (DOL, 2017). However, other countries, such as Japan, have classified soluble platinum as an airway and a skin sensitiser to indicate that it can induce respiratory and dermal sensitisation (JSOH, 2013). It is important to note that the absence of a sensitisation notation does not indicate the inability of the substance to produce sensitisation but rather that there is not enough conclusive evidence available to warrant such a notation (ACGIH, 2007).

2.6.3 Legislation applicable to dermal exposure

Quantitative dermal exposure limits or standards are more complicated than inhalation exposure limits because, in addition to exposure concentration and exposure time, the skin surface area and transfer rates from contaminated surfaces need to be taken into account as well (McDougal and Boeniger, 2002). An additional complication is the tremendous variety of exposure scenarios and ways in which workers can be exposed via the dermal pathway (Fenske, 1993; Schneider *et al.*, 2000). No legally binding dermal exposure limits are available although some approaches for the development of quantitative dermal exposure limits have been proposed in the past (Fenske, 1993; Bos *et al.,* 1998; McDougal and Boeniger, 2002). Another approach includes the communication of the risks and danger involved with handling certain chemicals (Cherrie *et al.*, 2010). In Europe, the REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) Regulation requires that information be provided on the risks

presented by chemicals (such as the adverse skin effects) throughout the supply chain as well as the manner in which they should be handled. They, therefore, promote risk management and the safe use of chemicals. In the USA, the OSHA has regulatory statutes that affect occupational dermal exposure. These include standards on skin notations, hand washing facilities, the use of PPE and the identification and communication of hazards to employees. Other legislation applicable to occupational dermal exposure include the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), which provides a criteria for the classification, packaging and labelling of hazardous substances. With GHS, substances that are relevant to skin exposure are classified with hazard statements or risk phrases. Furthermore, precautionary measures are provided to encourage the safe handling of hazardous substances. Although GHS is not legally binding, many countries have published regulations involving its implementation (IPCS, 2014). If a task involves skin contact with substances that are labelled with one or more of the relevant skin hazard risk phrases, then exposure should be assessed and, if necessary, control measures implemented (Cherrie *et al.*, 2010).

2.6.4 The skin notation

Skin notations were first used by the ACGIH in 1961 as risk indicators to communicate the significance of skin absorption (Boeniger, 2003). The skin notation is a qualitative measure used to indicate that dermal absorption of a chemical has the potential to contribute significantly to overall exposure (McDougal and Boeniger, 2002; Du Plessis *et al.*, 2008; DOL, 2017). The main purpose of the skin notation is to alert employers and occupational hygienists of the fact that skin absorption might occur following dermal exposure to the specific compound and that special precautions need to be implemented to prevent skin contact. (Sartorelli, 2002; HSE, 2011). In South Africa, the Hazardous Chemical Substances Regulations lists 174 substances (Du Plessis *et al.*, 2008; DOL, 2017) and the Mine Health and Safety Act Regulation 22.9 lists 117 substances with skin notations (Du Plessis *et al.*, 2008; DMR, 2017; DOL, 2017). In the USA, the ACGIH lists 190 substances and the OSHA lists 147 (IPCS, 2014) while in the UK, the HSE also lists over 120 chemicals with skin notations (Cherrie *et al.*, 2010; HSE, 2011). In 2009, NIOSH published a new strategy for assigning new skin notations. This strategy allows for the differentiation between chemicals that cause systemic, direct or sensitising effects following skin exposure. The strategy was revised in 2017 to clarify the levels of evidence for skin designations so that the overall completeness and quality of assembled data sets can be assessed (Schulte *et al.*, 2017). The reader is referred to the *Current Intelligence Bulletin 61: A strategy for assessing new NIOSH skin notations* (Schulte *et al.*, 2017) for detailed information on the NIOSH skin notations.

Soluble platinum is not listed with a skin notation in any of these regulations (HSE, 2011; ACGIH, 2017; DMR, 2017; DOL, 2017; OSHA, 2017). If there is no substantial information available regarding the dermal absorption of a chemical, such as is the case with soluble platinum, it might not be assigned a skin notation. However, this does not necessarily mean that no toxicity will occur if dermal exposure to that chemical takes place (McDougal and Boeniger, 2002; IPCS, 2014). It has recently been demonstrated that small amounts of soluble platinum can permeate through the skin and even though soluble platinum is not listed with a skin notation, there is a possibility that workers might develop adverse health effects following dermal exposure (Franken *et al.*, 2014).

The reader is referred to the Environmental Health Criteria 242 for dermal exposure compiled by the International Programme on Chemical Safety (IPCS, 2014) as well as publications by McDougal and Boeniger (2002) and Sartorelli (2002) for more information regarding dermal exposure measurements and the background and use of skin notations and dermal exposure limits.

2.6.5 Biological exposure index

Biological exposure indices (BEIs®) are used to evaluate a worker's total exposure to a substance via all exposure pathways, as it is an indicator of the total uptake of a substance (ACGIH, 2017). BEIs®, in most cases, represent the concentration of a contaminant in a biological matrix (e.g. platinum in urine) or metabolite which is likely to be observed in a healthy worker who was exposed via inhalation to a substance at the same level as the OEL (Angerer *et al.*, 2007; ACGIH, 2017). There is no BEI® value for platinum (ACGIH, 2017; DOL, 2017). Therefore, the concentration of urinary platinum measured in biological monitoring studies can only be compared to reference values from the general population or previous studies in occupational settings (CDC, 2017).

2.7 Summary of literature study

This literature study elucidated the background of occupational exposure to platinum compounds and its relevance to the workforce of South African precious metals refineries. The mining, refining and use of platinum compounds in various industries were described. Occupational exposure to platinum compounds via various exposure routes as well as the use of skin wipe sampling methods to assess occupational dermal exposure to metals was described. Additionally, the complexity of dermal exposure and the unknown effect of dermal exposure on the total platinum body burden and the development of sensitisation and other adverse health effects were highlighted. Furthermore, the use of biological monitoring to access occupational and environmental exposure via all routes of exposure was discussed. The

absorption, distribution and excretion of platinum in the human body were described and sensitisation as the main adverse health effect associated with exposure to soluble platinum was presented in detail. Finally, the legislative aspects of occupational exposure to platinum compounds were elucidated.

As is summarised in Chapter 3 of this thesis, numerous studies have reported the occupational respiratory exposure to soluble platinum experienced by precious metals refinery workers from various countries (including South Africa) (Calverley *et al*., 1995; Maynard *et al*., 1997; Heederik *et al*., 2016). However, the urinary platinum excretion of workers has only been reported for precious metals refineries in the UK and Europe (Farago *et al*., 1998; Schierl *et al*., 1998). Chapter 4 of this thesis reports the urinary platinum excretion of workers from two South African precious metals refineries. Even though occupational exposure to soluble platinum has been associated with adverse skin conditions, the dermal exposure experienced by precious metals refinery workers is not yet known. Additionally, it is not understood whether dermal exposure is correlated with the urinary platinum excretion of workers, although respiratory exposure has been correlated with urinary platinum excretion. Chapter 5 of this thesis will, for the first time report the dermal exposure of precious metals refinery workers to soluble platinum and investigate the involvement of the respiratory and dermal exposure routes in determining platinum body burden of workers, as indicated by their urinary platinum excretion.

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CHAPTER 3: ARTICLE I

Linde, S.J.L., Franken, A., Du Plessis, J.L. (2017) Occupational respiratory exposure to platinum group metals: A review and recommendations. *Chem. Res. Toxicol.*:30, 1778–1790.

3.1 Background

Inhalation is considered the primary route of exposure to platinum group metals (PGMs) in occupational settings. Airborne concentrations of platinum compounds have been measured in precious metals refineries since 1945 and are regularly assessed for legislative compliance purposes. The need was identified to review the information available on the occupational respiratory exposure to PGMs in order to assess the current state of knowledge. This article is a review of the published literature reporting respiratory exposure to PGMs. It summarises the concentrations of airborne platinum compounds reported in various occupational settings, methods used to assess exposure, the adverse health effects reported following occupational exposure as well as legislative aspects. This review article was published in *Chemical Research in Toxicology* and is available at http://pubs.acs.org/doi/full/10.1021/acs.chemrestox.7b00184.

Chemical Research in Toxicology publishes Articles, Reviews, Perspectives, and Chemical Profiles. The Journal is intended to provide a venue for presentation of research relevant to all aspects of the chemical basis of toxic responses. It emphasizes rigorous chemical standards and encourages application of modern techniques of chemical analysis to mechanisms of toxicity. Reviews may be comprehensive surveys of a broad range of literature with the intent of familiarizing the general reader with the current knowledge of a topic of active interest.

3.2 Occupational Respiratory Exposure to Platinum Group Metals: A Review and Recommendations

Chemical Research in Toxicology

Review

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Occupational Respiratory Exposure to Platinum Group Metals: A Review and Recommendations

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ABSTRACT: Platinum group metals (PGMs) is a group of metals that include platinum, palladium, rhodium, ruthenium, iridium, and osmium. Occupational respiratory exposure to platinum has been reported since 1945, but studies investigating occupational exposure to palladium, rhodium, ruthenium, iridium, and osmium are scarce. This review provides a summation of the information available on the respiratory exposure to PGMs in various industrial settings, methods used to assess exposure, and the possible adverse health effects resulting from occupational exposure to PGMs. Of these effects, respiratory sensitization caused by soluble PGMs is of most importance. Metallic PGMs have not been shown to cause allergic reactions. This review reiterates that occupational respiratory exposure to PGMs is dependent on the type of industry where exposure takes place, the chemical form (soluble or insoluble) of the PGMs present in the workplace air, and the tasks performed by workers in the specific work areas. Sensitization to soluble platinum is associated with the degree of exposure to soluble platinum compounds, and the highest concentrations of soluble PGMs in workplace air have been reported for precious metals refineries where personal exposures frequently exceed the occupational exposure limit for soluble platinum (2 $\mu g/m^3$). Additionally, this review emphasizes that personal exposure monitoring is preferred over area monitoring when assessing workers' exposure to PGMs. The legislation applicable to occupational exposure to PGMs is also discussed, and it is highlighted that the occupational exposure limit for soluble platinum has remained unchanged, in most countries, since 1970 and that too few countries have classified PGM compounds as respiratory or skin sensitizers. Finally, recommendations are made to ensure that future investigations are comparable in terms of the type of exposure monitoring (personal or area) conducted, the type of tasks included in the exposure monitoring program, and the format in which results are reported.

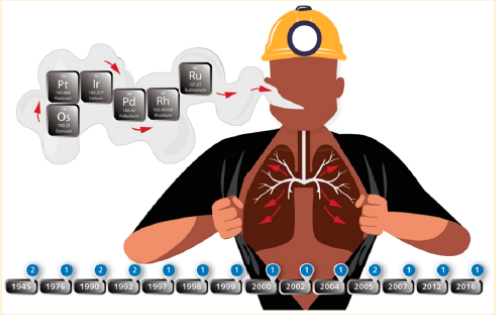

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Table 1. Summary of Health Effects Caused by Individual Soluble PGMs in Occupational Settings

		diagnosis	health effect				
PGM	industry	positive skin prick or patch test	respiratory sensitization/ asthma	rhinitis, tight chest, sneezing, shortness of breath	allergic contact dermatitis	other skin adverse effects	reference
Pt	handling paper treated with complex Pt salts in a photographic studio			X			12, 30
	PGM refinery		X	X	X	X	12, 31
	PGM refinery and laboratory	X	X		X		32
	secondary PGM refinery		X		X		33
	automotive catalyst production	X	X	X	X		34
	automotive catalyst production	X	X	X		X	35
	industrial exposure to chloroplatinates	X	X		X		36
	PGM refinery	X	X				27
Pd	PGM refinery	X	X				4, 37
	PGM refinery		X			X	4, 38
	automotive catalyst production	X	X				4
	chemist and metal workers				X		4
	metal coating	X	X	X			4, 39
	palladium chloride ($PdCl_2$) fumes from an electrolysis bath		X	X			16
	direct contact with Pd compounds	X	X				16
Rh	Rh plating at a goldsmith	X			X		40, 41
	electrochemical factory	X	X	X			17
	refining, jewelry and dental industries	X			X	X	13, 36
Ir	electrochemical factory	X	X	X		X	17, 42

1. BACKGROUND

Platinum group metals (PGMs) is a group of rare metals that include platinum (Pt), palladium (Pd), rhodium (Rh), ruthenium (Ru), iridium (Ir), and osmium (Os).[1] The main deposits of PGMs are found in South Africa, Russia, Zimbabwe, the United States of America, Canada, and China.[2,3] PGMs occur together naturally and are commonly used in automotive emission control catalysts, dental appliances, electrical appliances, jewelry, and anticancer drugs.[2,4,5] An increase in the use of automotive catalytic converters and the increased demand for electronic devices in the technologically developing world have resulted in an increase in the demand for these metals worldwide.[3,6] Particularly Pt, Pd, and Rh have become valuable commodities as they are widely used as automobile exhaust catalysts to convert noxious gas emissions into more benign forms.[7] Tighter European Union emission limits and higher diesel automobile output have led to an increased demand for Pt in the automotive industry with the total demand for Pt in the European automotive sector forecast to rise by 7% in 2017 (the highest level since 2008), and the worldwide demand for Pt in automotive catalysts is forecast to rise by 2%. The demand for Pd is forecast to rise by 5%, mainly due to the automotive catalyst industry, while the demand for Rh in the automotive catalyst industry as well as industrial applications such as the glass, chemical, and electrical sectors is also forecast to rise by 2−3%.[8]

To meet worldwide demands, workers in different industries such as mining, refining, catalyst production, chemical manufacturing, recycling, and the petroleum industry are exposed to PGMs on a daily basis.[9−11] Workers in these industries are, therefore, at risk of developing adverse health effects associated with exposure to PGMs. These effects are well documented and may include occupational asthma, rhinitis, tight chest, sneezing, shortness of breath, or allergic contact dermatitis.[4,12−14] Some of the PGM salts, such as the hexachloroplatinates, are among the most potent sensitizers and allergens encountered in the workplace, and respiratory sensitization to PGM-salts is a significant health problem in the PGM-industry.[15−17]

Occupational exposure to PGMs occurs mainly through inhalation,[10] and this review aims to give a critical review of published studies on the respiratory exposure to PGMs in occupational settings. Studies that reported area or personal occupational respiratory exposure to PGMs are reviewed to highlight differences in methodologies used, exposure levels in different industries, reporting methods, and other factors that may influence occupational respiratory exposure to PGMs. Furthermore, recommendations are made for future studies to promote, among other things, consistent reporting of results and to facilitate comparisons between studies. The main aim of this review is not to discuss, in detail, PGM toxicology, adverse health effects caused by PGM exposure, or environmental exposure to PGMs but to review occupational respiratory exposure to PGMs. Therefore, the topics mentioned above are only discussed briefly. For more information regarding these subjects, the reader is referred to reviews published by the World Health Organization,[12] the UK Foods Standards Agency: The Committee on Toxicology,[18] the European Commission Scientific Committee on Occupational Exposure Limits for Pt and Pt compounds,[19] the Dutch Expert Committee on Occupational Standards,[20] and the chapters on Pt[10], Pd[11], Rh[9], and Ir[21] in the *Handbook on the Toxicology of Metals, Volume II*.[22]

2. REVIEW METHOD

Literature searches were performed using Scopus, Google Scholar, and Science Direct with the search terms "platinum group metals", "occupational respiratory exposure to platinum group metals", "soluble platinum", "platinum salt sensitization", "platinum occupational exposure limit", "soluble rhodium", "soluble palladium", "soluble iridium", "soluble ruthenium", and "soluble osmium". All publications up to May 31, 2017 were considered. This review includes publications that investigated occupational respiratory exposure to PGMs in primary or

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secondary PGM industries. Publications examining respiratory exposure to PGMs resulting from environmental sources such as automotive emissions or road dust, PGM exposure in the dental industry, or exposure to antineoplastic drugs were excluded.

3. ROUTES OF EXPOSURE

Inhalation of PGM containing particulate matter is of greater significance in terms of potential health risks compared to ingestion as a route of exposure.[7] The respiratory tract shows a higher PGM uptake compared to the digestive tract,[23] and since inhalation is seen as the primary route of exposure to Pt salts, the majority of research regarding exposure has been performed on respiratory exposure. However, Maynard et al.[24] suggested that the skin as a route of exposure might serve as an alternative exposure route for Pt salts, and *in vitro* permeation studies have shown that Pt is permeable through intact human skin.[25,26] Heederik et al.[27] also stated that dermal exposure could be considered as an additional route of exposure in more comprehensive exposure assessments as it is unclear whether it plays a role in sensitization to Pt salts.

The main routes for occupational exposure to Pd, Rh, and Ir are via inhalation and, to a lesser extent, the skin. Absorption through inhalation is of particular importance in the refining and automotive catalyst industries.[9,16] Similarly to Pt, *in vitro* permeation studies have also shown that Pd nanoparticles[28] and Rh are permeable through intact human skin,[25,26,29] which suggests that the skin as a route of exposure may contribute to the total body burden of PGMs.

Table 1 summarizes the adverse health effects reported following occupational PGM exposure and contains examples of studies where adverse health effects or diseases of the respiratory tract and skin were reported following exposure to PGMs in various industries. This suggests that both the respiratory pathway and the skin must be considered as possible routes of exposure when investigating occupational PGM exposure.

4. TOXICOLOGY AND HEALTH EFFECTS

Sensitization to the different soluble PGMs and their effect on the immune system is the most important hazard to the health of humans.[16,17,27] These and other adverse respiratory (rhinitis, tight chest, sneezing, shortness of breath) and skin (eczema, urticaria) health effects caused by exposure to PGMs as well as instances where positive skin prick or patch tests were observed and are summarized in Table 1. Ru and Os were not included in Table 1 due to a lack of information available.

4.1. Platinum. The acute toxic effects of PGMs are dependent on metal speciation.[7,43] Toxicity evaluations of Pt have made distinctions between the toxicity of Pt and its salts on the one hand and the toxicity of Pt complexes that have medicinal (i.e., cis-platinum) or industrial applications (i.e., fuel catalysts) on the other.[18] The metallic form of Pt is considered to be biologically inert and nonallergenic,[1,2] and there is no evidence of sensitization or adverse health effects.[12] On the contrary, some Pt salts, such as hexachloroplatinates and tetrachloroplatinates, are among the most potent sensitizers and allergens known[2] and represent the most hazardous chemical forms of Pt.[35] The allergic symptoms suffered by sensitized workers indicate a type I reaction mediated by IgE,[27] and it is estimated that 1% of workers exposed to chloroplatinic acid worldwide become sensitized annually. This usually leads to their permanent removal from even very low, short exposure and often removal from employment within the Pt industry.[15] Although the exact exposure circumstances that cause sensitization, or the risk factors for developing sensitization, are not yet known,[6,15] many studies have identified respiratory exposure to Pt salts, smoking[27,33,34,44,45] and atopy[27] as risk factors for the development of Pt salt sensitization. These studies demonstrated the link between the degree of respiratory exposure to Pt salts and the occurrence of Pt salt sensitivity and, therefore, highlight the need to quantify the concentration of Pt salts in workplace air to estimate the risk for sensitization.

4.2. Palladium. Epidemiological studies have shown that Pd ions are frequent reacting sensitizers.[16] Chemical and refinery workers are exposed to Pd salts during their daily tasks, which may cause primary respiratory, skin, and eye irritations.[4] Adverse health effects due to inhalation exposure and direct contact to palladium chloride have also been reported.[16] However, the UK Foods Standards Agency: Committee on Toxicology[18] stated that the Hazardous Substances Data Bank reported that despite the wide use of Pd, no occupational diseases have been shown. The lack of data on disease due to occupational exposure to Pd is reflected in the fact that only Finland has set an occupational exposure limit (OEL) for Pd.[46]

4.3. Other PGMs. Information on adverse health effects caused by the lesser known PGMs (i.e., Rh, Ir, Ru, and Os) is rare, and only a few cases of allergic reactions to Rh and Ir have been reported[9,13,17,41,42] (see Table 1). Positive skin prick test reactions for Rh have been reported in refinery and catalyst production workers.[9] In a case report by Merget et al.,[17] an atopic operator in an electroplating plant had positive skin prick tests for Rh and Pt following exposure to Rh salts. Since the sensitivity to the Rh salt was much higher, the authors concluded that Rh salts should be considered as occupational immediate-type allergens. De la Caudra and Grau-Massanés[41] and Goossens et al.[13] also published case reports of three workers (two jewelers and one refinery worker) who presented with occupational allergic contact dermatitis caused by Rh solutions or powders. Another case study reported Ir induced allergic occupational asthma where the diagnosis of Ir salt allergy was made in an electrochemical factory worker who was exposed to iridium chloride.[17,42]

5. EXPOSURE-RESPONSE AND CONSEQUENCE OF SENSITIZATION

The risk of developing hypersensitivity to soluble PGMs is predominantly correlated with intensity or degree of exposure.[47] Positive hypersensitivity reactions obtained by Santucci et al.[47] were only found in occupationally exposed workers and were not seen in nonoccupationally exposed people living in urban areas. Other studies have also shown that the degree of exposure to soluble Pt is associated with the development of Pt salt sensitivity.[27,34,45] In general, the practice is to remove workers from areas of high exposure once they are sensitized to soluble PGMs. However, removing workers from areas of soluble Pt exposure does not necessarily mean that symptoms of occupational asthma will cease.[14,27,48] Merget et al.[14] showed that removing workers from areas where they are exposed to soluble Pt after they have already developed respiratory symptoms does not always prevent chronic asthma later in life. They recommended that removal from exposure should be done immediately following positive skin prick tests, irrespective of symptoms. However, since the degree of exposure to soluble Pt plays a significant role in the development of sensitization,[27] more emphasis should be placed on reducing the exposure of workers to soluble PGMs to as low as reasonably practicable

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Table 2. Summary of Inhalable Fraction Sampling Methods Used To Measure Personal Respiratory Exposure to PGMs[a]

method	sampling media and pore size	sampling head and flow rate	analytical technique	LOD	reference
OSHA ID-130SG Pt in workplace atmospheres	MCE 0.8 μm	Cassette 2 L/min	AAS-GF	0.01 μg/mL	20, 59, 66
MDHS 46/2 Pt metal and soluble Pt compounds in air	MCE 0.8 μm	IOM sampler[b] 2 L/min	ICP-MS or AAS-GF	1−4 μg/m^3 (30 L air sample)	20, 60, 66
OSHA ID-121 Metal and metalloid particles in workplace atmospheres (atomic absorption)	MCE 0.8 μm	Cassette 2 L/min	ICP-AES or AAS-GF	2 μg/mL	61, 66
NIOSH 7303 Elements (incl. Pt and Pd) by ICP (Hot block/HCl/HNO_3 digestion)	MCE 0.8 μm	Cassette 1−4 L/min	ICP-AES	0.38 (Pt) 0.75 (Pd) μg/sample	20, 62
NIOSH 7302 Elements (incl. Pt) by ICP (Microwave digestion)	MCE 0.8 μm	Cassette 1−4 L/min	ICP-AES	8 μg/sample	63
NIOSH 7304 Elements (incl. Pt) by ICP (microwave digestion)	PVC 5.0 μm	Cassette 1−4 L/min	ICP-AES	9 μg/sample	67
IPA Harmonized Methodology for the Sampling of Pt in Workplace Atmospheres	MCE 0.8 μm	IOM sampler 2 L/min	ICP-MS	0.00008 μg per sample or 0.0027 μg/m^3 (30 l air sample)	64, 66

[a]LOD, limit of detection; MDHS, Methods for Determination of Hazardous Substances; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; MCE, mixed cellulose ester; PVC, poly vinyl chloride; AAS-GF, graphite furnace atomic absorption spectrometry; ICP-MS, inductively coupled plasma-mass spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectroscopy; HSE, Health and Safety Executive; IPA, International Platinum Group Metals Association; IOM, Institute for Occupational Medicine. [b]IOM inhalable sampler, multiorifice inhalable sampler, or conical inhalable sampler may be used.

through proper use of engineering controls and the optimization of work methods. By automating processes and reducing manual handling of material, workers' exposure to soluble Pt can be reduced along with the risk of becoming sensitized, which will also reduce the number of workers who need to be removed from the workplace as a result of becoming sensitized. Hunter et al.[31] suggested that asthma caused by complex Pt salts could be prevented by not allowing these salts to reach the workplace atmosphere and that this could be achieved by the effective use of exhaust ventilation. The highest exposure to Pt listed in the published literature (5000−80 000 μg/m^3) was recorded in an extremely poor ventilated refinery in China where workers were exposed to dust and spray of complex Pt salts and Pt metal.[19,49,50] This, along with evidence that the degree of exposure increases the risk for sensitization,[27,34,45] suggests that reducing workers' exposure to Pt salts through proper control measures is the best way to reduce the occurrence of sensitization to Pt salts.

6. OCCUPATIONAL EXPOSURE

6.1. Platinum. There are three primary categories of industrial sources for exposure to Pt, namely mining, refining, and processing,[50] and investigations into workers' occupational exposure to Pt salts have been conducted since 1945.[31,51] The information available regarding the effects of PGMs in humans was predominantly provided by occupational exposures in precious metals refineries;[27,33,45,52] however, with the increased production of automotive catalysts, investigations have also been conducted in the automotive catalyst production industry.[6,34,53] Significant respiratory exposure to Pt compounds has been reported in production areas of refineries and automotive catalyst plants,[45] and even though the concentrations of Pt reported for nonproduction areas are lower than those obtained in production areas, they are still much higher than those reported for distant (nonexposure) areas.[6]

6.2. Other PGMs. Only a few studies have reported occupational respiratory exposure to Pd, Rh, and Ir in refineries or automotive catalyst plants.[6,51,54−56] One study of note is Cristaudo et al.,[6] which reported Pt, Pd, Rh, and Ir concentrations in workplace air in an automotive catalyst production and recycling plant. Their results for personal exposure ranged between 0.003 and 5.75 μg/m^3 for Pd, between 0.0001 and 0.035 μg/m^3 for Rh, and between 0.00006 and 0.002 μg/m^3 for Ir. Cristaudo et al.[35] reported that the prevalence of positive skin prick tests for Pd, Rh, and Ir in an automotive catalyst manufacturing plant was very low and, during their investigation, only workers who were sensitive to Pt tested positive. Some studies have identified Pd allergies in refineries and automotive catalyst manufacturing plants,[4] and Rh- and Ir-allergies have been identified in electrochemical and jewelry industries where workers came into close contact with solutions containing Rh or Ir.[17,41]

The findings from studies reporting occupational respiratory exposure to PGMs will be discussed in detail during later sections.

7. NONOCCUPATIONAL EXPOSURE

Although the concentrations of Pt measured in nonproduction areas of industrial plants are much lower than those measured in production areas, they are still 1000-times higher than concentrations measured in distant nonindustrial areas.[53] In comparison to concentrations of soluble Pt in the indoor air of various workplaces, which is normally measured at μg/m^3 levels, the soluble Pt contents of environmental samples measured in cities are usually in the pg/m^3 range.[2] The increased use of PGMs as automotive catalysts has sparked interest in environmental exposure experienced by the general public and occupations such as tram drivers.[57] It has been demonstrated that the PGM concentrations present in airborne particulate matter in urban settings are significantly higher than that of rural settings where there are fewer emission sources,[58] and over recent decades, the Pt, Pd, and Rh contents of airborne particulate matter in major cities have increased substantially.[9,10,16] The general population can also be exposed to low concentrations of Pt and Pd through jewelry and mucosal contact with dental restorations.[4,10] Nevertheless, it is unlikely that people from the general population, who are exposed to ambient concentrations of soluble PGMs at least three orders of magnitude lower than as seen in occupational settings, will develop similar adverse health effects.[12]

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8. EXPOSURE ASSESSMENT AND ANALYSIS METHODOLOGY

In 1945, Hunter et al.[31] and Fothergill et al.[51] collected airborne particulate samples in precious metals refineries by drawing a known volume of air through a particulate filter during specific tasks or operations. These samples collected soluble Pt salts and Pt metal as well as other precious metals. For analysis, Hunter et al.[31] used a colorimetric method, while Fothergill et al.[51] used a combined chemical and spectrographic method. These two methods were used at the same sampling points in one of the refineries, and similar results were obtained.[31] Over 30 years later, Johnson et al.[54] reported Pt and Pd concentrations in environmental samples collected in mining and refinery areas on glass fiber filters with hi-volume air samplers, which sampled continuously over 14 days. Baker et al.[33] reported area Pt salt exposure from environmental monitoring data gathered between 1977 and 1979 in a secondary Pt refinery. However, the exact monitoring procedure was not disclosed.

In 1985, the Occupational Safety and Health Administration (OSHA) and the Health and Safety Executive (HSE) published methods [OSHA ID-130SG and Methods for the Determination of Hazardous Substances (MDHS) 46, respectively] for the determination of exposure to Pt in workplace atmospheres.[59,60] Since then, the measurement of soluble Pt or Pt metal in workplace air has involved drawing air at approximately 2 L/min through a mixed cellulose ester (MCE) filter, which is connected to a sampler designed to collect the inhalable particulate fraction.[59−64] It must be noted, however, that methods such as the MDHS 46 cannot differentiate between different chemical species, which might be problematic since different chemical species of soluble Pt are more potent allergens compared to others.[65] Since 1985, the HSE has published the updated MDHS 46/2 method, and the OSHA and the National Institute for Occupational Safety and Health (NIOSH) have published methods for the determination of exposure to metals or elements (including Pt and Pd) in workplace air.[61−63,66] The most recent guideline methodology for the measurement of Pt in workplace air was described by the International Platinum Group Metals Association (IPA).[64] Table 2 summarizes the sampling methods available to determine personal exposure to soluble and insoluble Pt compounds in workplace air.

Analytical methods such as graphite furnace atomic absorption spectrometry (AAS-GF), inductively coupled plasma-mass spectrometry (ICP-MS), and inductively coupled plasma-atomic emission spectroscopy (ICP-AES) have been used to quantify Pt compounds in various media.[12,63] Most of the available methods are only validated for the analysis of Pt, while the NIOSH 7303 method is validated for Pt and Pd.[62] As indicated in Table 2, the limit of detection (LOD) differs for all of the available methods with the sensitivity of the methods increasing with time. For example, the MDHS 46/2 method, published in 1996, reported a LOD for Pt of 1−4 $\mu g/m^3$ for a 30 L air sample (15 min at 2 l/min), while the IPA Harmonized Methodology for the Sampling of Pt in Workplace Atmospheres, published 20 years later, reported a LOD of 0.0027 $\mu g/m^3$ for a 30 L air sample.[60,64,66]

9. AREA VERSUS PERSONAL MEASUREMENTS

The methodologies listed in Table 2 can be used to determine personal exposure of workers to PGM compounds. Various PGM exposure investigations have also collected area measurements where the concentration of PGMs in the general workroom air was determined.[6,34,68] Cristaudo et al.[6] described area and personal measurements collected in different areas of an automotive catalyst production plant. Correlations performed between the PGM content of area measurements and personal measurements revealed very strong positive correlations for Pt ($r = 0.983$, $p < 0.001$) and Pd ($r = 0.961$, $p < 0.001$). A similar observation was made by Vos et al.[68] where the refinery worker with the highest personal soluble Pt exposure was working in the area where the highest area soluble Pt concentration was measured. Nevertheless, Vos et al.[68] reported that the mean area soluble Pt concentrations (0.583 $\mu g/m^3$) were significantly lower than mean personal exposures to soluble Pt (1.813 $\mu g/m^3$) for tasks where personal and area measurements were collected simultaneously. Subsequently, the authors concluded that area soluble Pt concentrations were not an effective indicator of personal exposure. Merget et al.[34] also reported higher Pt concentrations for personal sampling compared to area sampling, and mean concentrations of Rh in personal measurements (0.035 $\mu g/m^3$) collected by Cristaudo et al.[6] in the coating department was much higher than that of area measurements (0.002 $\mu g/m^3$). These studies indicate that area measurements cannot be used to indicate personal exposure and that personal exposure measurements are preferred when assessing workers' exposure to PGMs. Collecting personal exposure measurements instead of area measurements also provides the investigator with the extra benefit of being able to compare the exposures to the OEL.

10. OCCUPATIONAL EXPOSURE LIMITS (OELS) AND ASSOCIATED NOTATIONS

10.1. Soluble Platinum. In 1963, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted the threshold limit value-time weighted average (TLV-TWA) for soluble Pt salts of 2 $\mu g/m^3$, over an 8-h shift. In 1970, it was revised to the TLV-TWA of 2 $\mu g/m^3$, for soluble Pt salts (measured as Pt), which is presently still in use.[27,69] The same exposure limit has been used by the OSHA (United States of America) as permissible exposure limit (PEL) since as early as 1974.[70] Currently, most countries with a Pt industry still impose this 8-h time weighted average (TWA) respiratory OEL of 2 $\mu g/m^3$ for water-soluble Pt species. Although it is one of the lowest limits for workplace respiratory chemical exposure,[15] sensitization was reported to be occurring at concentrations below 2 $\mu g/m^3$ and as a result, in 1991, a World Health Organization (WHO) task group considered recommending an even lower OEL. However, there was not sufficient exposure-response data available to justify a reduction in the OEL and they, subsequently, recommended that the OEL of 2 $\mu g/m^3$ be changed from an 8-h TWA to a ceiling value, which may not be exceeded at any time during the shift.[12]

In 2000, the Japan Society for Occupational Health (JSOH) established a TWA-OEL of 1 $\mu g/m^3$ for soluble Pt (as Pt),[71] and in 2008, the Dutch Expert Committee on Occupational Standards (DECOS) recommended a health-based 8-h TWA-OEL of 5 ng/m^3 (as Pt) for chloroplatinates as inhalable dust.[20,27] Despite some species of soluble Pt (i.e., chloroplatinates) being more potent allergens compared to others, most countries/organizations list the OEL of 2 $\mu g/m^3$ as being applicable to "soluble Pt salts".[65] The HSE (United Kingdom), however, does not use a generic description in its list of workplace exposure limits (WELs). Instead, they exclude certain halogeno-Pt compounds from the classification of soluble Pt compounds as they are not potent sensitizers.[65,72]

A number of studies have reported that respiratory exposures of workers frequently exceeded the OEL of 2 $\mu g/m^3$, and it is

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possible that this workplace limit alone is not completely protective and that sensitization can occur at exposure levels much lower than the OEL.[12,15,24,27,45,65,68] Because of this, the DECOS proposed an 8-h TWA-OEL for chlorinated Pt salts of 5 ng/m^3, which is 400-times lower than the current OEL.[15,20,27] This recommendation was based solely on a 5-year prospective cohort study by Merget et al.[34] and has sparked controversy because the authors, themselves, stated that the results from the study could not be used to define a valid cutoff value for an OEL.[15,27] Since occupational exposure to soluble Pt still frequently exceeds the OEL,[27,68] it seems unlikely that high exposure industries, such as refineries, will be able to comply with the proposed OEL. However, the fact that the OEL for soluble Pt has remained unchanged since 1970 questions whether the limit is still relevant and whether it is capable of protecting workers from developing adverse health effects. This has led the IPA and its member companies to implement a best practice exposure limit of 0.1 μg/m^3 for soluble Pt exposure to better protect their workers from the adverse health effects associated with exposure to soluble Pt (Cas Badenhorst, personal communication).

Table 3 gives a summary of the countries which have used sensitization notations to classify soluble Pt compounds as respiratory or skin sensitizers. Only seven of 20 countries or organizations, included in this review, have classified soluble Pt compounds as sensitizers. However, the manners in which countries classify chemicals as sensitizers differ from one another in that some countries only classify respiratory sensitizers, while others acknowledge that chemicals can cause respiratory or skin sensitization but do not specify which chemical causes which type of sensitization, and others classify chemicals as either respiratory or skin sensitizers or as both.

Table 3. Summary of Countries/Organizations That Classify Soluble Pt as a Sensitizer

	type of sensitizing notation			
country/organization	respiratory	skin	not specific	reference
United Kingdom	X			72
South Africa	X			73, 74
Sweden			X	75
Canada (British Colombia)			X	76
Australia			X	77
Germany	X	X		78
Japan	X	X		71

10.2. Insoluble Platinum. The majority of countries, with the exception of the United Kingdom and South Africa (5 mg/m^3), have adopted an 8-h TWA-OEL of 1 mg/m^3 for insoluble Pt metal, which is considerably higher than that of soluble Pt compounds.[63,72,73,79] The reason for this is that exposure to metallic Pt has not been associated with the development of allergic symptoms or other diseases.[20]

In addition to a TWA-OEL for soluble Pt (2 μg/m^3) and Pt metal (5 mg/m^3), the Department of Minerals and Resources (DMR) in South Africa has set a TWA-OEL of 3 mg/m^3 for respirable Pt mine dust measured in Pt mines.[74]

10.3. Other PGMs. Finland is the only country that has assigned an OEL to Pd compounds (0.5 mg/m^3 for insoluble Pd and 1.5 μg/m^3 for soluble Pd),[46] and the German Research Foundation has classified palladium chloride as a skin sensitizer.[78]

In general, the TWA-OELs for insoluble (metallic) and soluble Rh compounds set by countries or organizations are lower than those for Pt compounds. Most countries or organizations have assigned a TWA-OEL of 1 μg/m^3 for soluble Rh compounds and 0.1 mg/m^3 for insoluble Rh compounds.[46,72−74,76] The German Research Foundation has classified Rh as a suspected carcinogen,[78] and the ACGIH has classified it as "non-classifiable as a human carcinogen due to a lack of evidence".[79] The JSOH has classified Rh as a substance that will probably induce allergic reactions in human skin.[71]

11. EXPOSURE STUDIES IN OCCUPATIONAL SETTINGS

Occupational exposure to airborne soluble Pt has been reported for a variety of workplaces, which include refineries, automotive catalyst production plants, recycling plants, and metal coating facilities.[10] Conversely, studies reporting occupational exposure to airborne Pd, Rh, and Ir are limited with only a few studies investigating occupational exposure to these metals.[6,53,54,56]

11.1. Platinum. Results from published studies investigating occupational respiratory exposure to soluble Pt were collated and compared in Figure 1 to show in which industries the highest concentrations of soluble Pt exposure were reported. For additional detailed information, the reader is referred the chapter on Pt[10] in the *Handbook on the toxicology of metals, Volume II*.[22] Studies included in Figure 1 report results from personal and area measurements collected in different industries. Only studies reporting soluble Pt concentrations were included since the soluble form produces greater adverse health effects.[10] Selected studies that reported occupational exposure to total (metallic and soluble) Pt, or that only reported the percentage of personal exposure measurements that exceeded the OEL or where a geometric mean could not be calculated were excluded from Figure 1. These studies are briefly discussed in the text only.

As is shown in Figure 1, the highest exposures to soluble Pt have occurred in refineries and respiratory exposures of refinery workers frequently exceeded the OEL of 2 μg/m^3.[27,45,68] Figure 1a shows personal exposures to soluble Pt as reported by the various exposure studies. In all of the investigations conducted in refineries (a−h), the maximum personal exposures exceeded the OEL of 2 μg/m^3 and most studies reported maximum exposures exceeding 10 times the OEL. All of the geometric means recorded for refineries in Figure 1a are below 0.05 μg/m^3, which suggest that, in refineries, the majority of personal exposures are low and that only a small percentage of measurements actually exceed the OEL, although those excursions can be over 50-times the OEL. The studies conducted solely in automotive catalyst production plants, recycling plants, and metal coating plants (i−l) reported much lower soluble Pt personal exposure results than those conducted in refineries.

Figure 1b contains concentrations of soluble Pt from area measurements as reported in various studies. Most of the geometric means for studies conducted in refineries (a−l) exceeded 2 μg/m^3, while all of the concentrations reported for automotive catalyst and recycling plants were below 2 μg/m^3.

The exposure studies that could not be included in Figure 1 are summarized in the following text:

(i) Johnson et al.[54] reported mean concentrations of total Pt from area measurements which were collected continuously over five working days. The measurements were collected in a Sudbury mine's precious metals area (0.377 μg/m^3) as well as the refinery section (0.159 μg/m^3) and in the salts section (0.180 μg/m^3) of a precious metals refinery.

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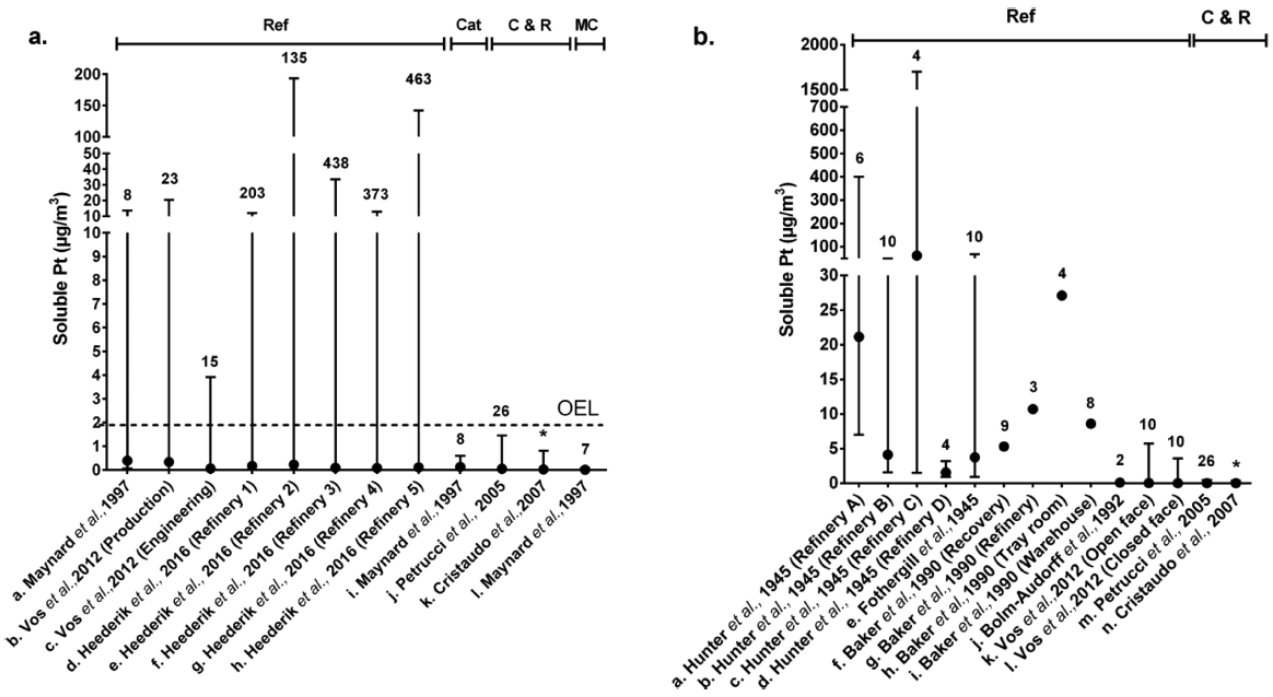

Figure 1. (a) Chronological summary of studies reporting personal exposure to soluble Pt in various industries as well as (b) area measurements of soluble Pt in different industries. The number of measurements collected during each study is indicated above each plot. * indicates that the number of measurements was not indicated in the study. ● indicates the geometric mean concentration. The upper and lower limits of the plots indicate the maximum and minimum values, respectively. The industries where the measurements were collected are indicated above the graph: Ref, refineries; Cat, catalysts production plants; C & R, catalyst production and recycling plants; MC, metal coating plants. Note that Baker et al.[33] (panel b) only reported the geometric means of results from different areas of the refinery without reporting minimum and maximum values. For Petrucci et al.[53] and Cristaudo et al.,[6] the mean percentage soluble fraction reported in the total airborne area samples for each work area was used to estimate the soluble Pt concentration of the personal measurements where only the total Pt concentrations in the total airborne fractions were reported.

(ii) Brooks et al.[48] investigated Pt salt sensitization among Pt refinery and recycling workers and reported that the OEL for soluble Pt (2 $\mu g/m^3$) was exceeded 50−70% of the time.

(iii) Schaller et al.[80] reported occupational exposure to total Pt in catalyst manufacturing and recycling industries. They reported mean concentrations of 5.1 $\mu g/m^3$ (range: 0.3−19.9 $\mu g/m^3$; $n = 19$) in the catalyst production area and 2.1 $\mu g/m^3$ (range: 1.8−3.1 $\mu g/m^3$; $n = 16$) in the mechanical treatment area.

(iv) Schierl et al.[81] conducted area and personal air sampling to determine workers' exposure to airborne Pt in a Pt refinery and catalyst production company. They reported mean concentrations of 1.1 $\mu g/m^3$ (range: 0.2−3.4 $\mu g/m^3$) for area measurements and 2.5 $\mu g/m^3$ (range: 0.8−7.5 $\mu g/m^3$) for personal measurements.

(v) Linnett and Hughes[65] investigated the potential of different soluble Pt species to provoke allergic reactions in refinery workers. They reported results from personal and area soluble Pt measurements collected in a PGM refinery, a tetraammine platinum trichloride (TPC) laboratory, and an automotive catalyst production plant. At the PGM refinery, 5.1% of 8573 measurements exceeded the OEL (2 $\mu g/m^3$), while at the TPC laboratory, 48.3% of 511 measurements, and 28.7% of the 453 measurements at the automotive catalyst production plant, exceeded the OEL. Although the soluble Pt exposures measured at the TPC laboratory and the automotive catalyst production plant were significantly higher compared to the PGM refinery, the incidence of chloroplatinate allergy at the PGM refinery was higher compared to the other areas. Therefore, the authors concluded that TPC is not allergenic under normal industrial conditions and that the specific species of soluble Pt is very important since it will influence the degree of the adverse health effects experienced by the workers.

(vi) Merget et al.[34] aimed to assess exposure to Pt salts and the incidence of Pt salt allergy in an automotive catalyst production plant and reported that 4% of 78 personal exposure measurements collected in high-exposure areas exceeded the OEL of 2 $\mu g/m^3$. In low exposure areas within the plant, they reported concentrations of below 10 ng/m^3 and 30−90 pg/m^3 in areas outside of the plant. Since no incidences of sensitization were observed in workers with low exposure, the authors concluded that exposure to concentrations of soluble Pt below 10 ng/m^3 might be considered safe.

11.2. Palladium, Rhodium, and Iridium. Although occupational exposure to Pd, Rh, and Ir originating from environmental sources such as road dust has been reported,[82] only a few studies have reported occupational exposure to soluble Pd, Rh, and Ir originating from industrial sources:

(i) Fothergill et al.[51] reported concentrations of airborne Pd ranging from 0.3−32 $\mu g/m^3$ (mean = 4.99 $\mu g/m^3$; $n = 10$) during various tasks in a precious metals refinery.

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(ii) Johnson et al.[54] reported a mean concentration of Pd in a Sudbury mine's precious metals area of 0.291 $\mu g/m^3$ as well as mean Pd concentrations from area measurements collected continuously over five working days in a precious metals refinery [0.085 $\mu g/m^3$ (refinery section) and 0.028 $\mu g/m^3$ (salts section)].

(iii) Kielhorn et al.[4] reported four personal exposure Pd measurements collected during the production of Pd compounds in 1996 (range: 0.38−11.6 $\mu g/m^3$). Another four Pd measurements were collected during 2000, two of which were short-term measurements (<0.5 and 3.1 $\mu g/m^3$) and two were 8-h TWA measurements (28 and 128 $\mu g/m^3$).

(iv) Petrucci et al.[55] reported concentrations of total PGMs in airborne particulate matter in various areas of an automotive catalyst production plant. The results ranged from 0.006−2.1 $\mu g/m^3$ for Pd, 0.001−0.003 $\mu g/m^3$ for Rh, and 0.00005−0.002 $\mu g/m^3$ for Ir.

(v) Violante et al.[56] and Cristaudo et al.[6] reported results of area measurements and personal exposure to the lesser known PGMs in various areas of an automotive catalyst production plant. Violante et al.[56] reported personal exposure to total Pd that ranged from 0.001−7.90 $\mu g/m^3$, while area Pd measurements ranged from 0.002−10.6 $\mu g/m^3$ for PM_{10} and from 0.03−11.0 $\mu g/m^3$ for total Pd. Cristaudo et al.[6] reported the mean personal measurements that ranged from 0.0001−0.035 $\mu g/m^3$ for total Rh and from 0.00006−0.002 $\mu g/m^3$ for total Ir. They also reported area PM_{10} measurements that ranged from 0.001−0.003 $\mu g/m^3$ for Rh and from 0.00005−0.002 $\mu g/m^3$ for Ir.

12. FACTORS THAT INFLUENCE OCCUPATIONAL RESPIRATORY EXPOSURE

Occupational respiratory exposure to PGMs can be influenced by a variety of factors such as the processes and tasks associated with the specific industry where exposure occurs and the chemical form to which workers are exposed.

12.1. Industry Types. The degree of exposure to PGM compounds differs between different industries. As is shown in Figure 1, the exposure to soluble Pt in refineries is generally higher than in catalyst production or chemical plants.[10,24,34] This is very well demonstrated by Maynard et al.[24] (studies a, i, and l in Figure 1a), who measured full shift (8 h) as well as task-based personal exposure to soluble Pt at a refinery, an automotive catalyst production plant, and a metal coating facility. The mean exposure results from the refinery (8-h = 2.163 $\mu g/m^3$; short-term = 2.531 $\mu g/m^3$) were considerably higher than that from the automotive catalyst production plant (8-h = 0.216 $\mu g/m^3$; short-term = 1.000 $\mu g/m^3$) or the metal coating facility (8-h = 0.017 $\mu g/m^3$; short-term = 0.090 $\mu g/m^3$). Only the measurements collected over 8 h are shown in Figure 1a.

12.2. Species. The soluble fraction of PGMs in airborne particulate matter in each work area can differ tremendously from one area to another and can impact the degree of exposure to soluble PGMs experienced by the workers.[53,56] Cristaudo et al.[6] (study k in Figure 1a) reported the highest exposure to Pt in the coating department, while the highest exposure to Pd was measured in the recycling and chemical catalyst departments. The mean soluble PGM fraction measured in all of these areas differed from one another. For example, the samples from the coating department contained 30.1% soluble Pt and 36.1% soluble Pd, and the samples from the chemical catalyst department contained 8% soluble Pt and 63.3% soluble Pd. This meant that workers in areas with PGMs that contained higher fractions of their soluble forms had an increased risk of exposure to soluble PGMs and PGM sensitization compared to other areas where higher fractions of the PGMs were insoluble. Furthermore, Linnett and Hughes[65] identified some soluble species of Pt to be more allergenic compared to others. Therefore, since the chemical form of Pt and other PGMs can have a substantial effect on the severity of the adverse health effects caused by exposure,[6,43,65] identifying the chemical species to which workers are exposed is of great importance when conducting investigations into occupational PGM exposure.

12.3. High Exposure Tasks and Areas. Hunter et al.[31] reported concentrations of Pt in different work areas in four precious metals refineries (studies a−d in Figure 1b). These area measurements ranged from 0.9−1700 $\mu g/m^3$ with the maximum measurement of 1700 $\mu g/m^3$ (study c in Figure 1b) recorded in an area where ammonium hexachloroplatinate was crushed. Fothergill et al.[51] reported airborne concentrations of Pt and Pd in different work areas of a precious metals refinery, which ranged from 0.9 to >68 $\mu g/m^3$ for Pt (study number e in Figure 1b) and from 0.3−32 $\mu g/m^3$ for Pd. The maximum concentration Pt was measured during discharging of ammonium hexachloroplatinate from drying ovens, and the maximum concentration Pd was measured during hand crushing and packing of diammine dichloropalladium. Both of these studies reported handling and crushing of dry salts as tasks where airborne concentrations were increased compared to other areas in the refinery. Hunter et al.[31] indicated that incidences where workers complained of asthma were the highest in areas where workers came into contact with complex Pt salts in their dry form. Calverley et al.[45] reported that 27% of 566 Pt salt exposure measurements collected from production workers in a refinery exceeded the OEL of 2 $\mu g/m^3$ and that none of the measurements collected from non-production occupations exceeded the OEL. In a more recent study conducted in a precious metals refinery during nonroutine operations, the personal exposure of production workers to soluble Pt ranged from 0.010−20.479 $\mu g/m^3$ (study b in Figure 1a) where the maximum concentrations occurred during cleaning activities (cleaning draft lines and glove boxes).[68] During the same study, engineering (study c in Figure 1a) workers were also exposed to soluble Pt (0.004−3.916 $\mu g/m^3$) during dismantling activities. In studies conducted in automotive catalyst production plants (studies j and k in Figure 1a), the highest concentrations of soluble Pt were recorded in the coating departments where Pt salt solutions were used to coat catalytic supports and impregnation areas where devices were impregnated with Pt salt.[6,34,53] Therefore, differences in the tasks performed in different working areas can have a substantial influence on exposure experienced by workers.

Heederik et al.[27] analyzed personal soluble Pt exposure measurements from five Pt refineries, retrospectively (studies d−h in Figure 1a). Between 135 and 463 measurements from each refinery were analyzed. The distribution of the results was highly skewed to the right, and two of the refineries' 95th percentile measurement was still below the OEL, while all five refineries' 75th percentiles were below half of the OEL. This showed that these refineries contained a few high exposure tasks or areas, while the majority of tasks or areas were associated with exposure below the OEL. Therefore, since the exposure profiles of different PGMs will differ between different work areas and during different activities, it is vital that workers with a variety of job titles, working in different work areas, performing routine and

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nonroutine tasks, be monitored during a PGM exposure investigation to identify high exposure tasks and to obtain an accurate representation of the exposure experienced by workers in the specific occupational setting.

13. DIFFERENCES IN REPORTING OF PGM EXPOSURE

Exposure data from available sources regarding PGM exposure in workplaces may not be directly comparable due to differences in sampling and analytical techniques.[50] It was apparent that the means in which research papers reported workers' respiratory exposure to PGMs differed from one another. Some papers focused on the medical surveillance of workers with Pt salt sensitivity and reported the percentage of personal or area soluble Pt measurements that exceeded the OEL of 2 $\mu g/m^3$,[45,48,65] or divided the workplaces into low and high exposure areas.[34] This made it difficult to compare the concentrations of soluble PGMs measured with other studies where minimum, maximum and mean values were reported.

Furthermore, styles of reporting which species of the individual PGMs (soluble or metal) were measured differed between studies. For example, some papers reported concentrations of the individual soluble PGM measured,[24] while others reported the concentrations of total individual PGM (metal and soluble), which were measured, along with the percentage of soluble species.[6,53] Other papers only reported concentrations of individual PGMs in the air of workplaces.[55]

Differences in the reporting of exposure data hinder the comparison of data with those of other studies. As a result, recommendations are made in the following section to promote uniform reporting of data and stimulate effective comparison of exposure data from various sources.

14. RECOMMENDATIONS

(i) Merget et al.[34] and Vos et al.[68] both collected personal and area measurements where the results from the personal exposure monitoring were higher compared to the results from the area monitoring, and Vos et al.[68] stated that results from area monitoring should not be used to predict personal exposure. It is, therefore, recommended that, if possible, personal exposure monitoring should be performed instead of area monitoring to get a more accurate representation of the exposure to soluble PGMs experienced by workers.

(ii) The concentrations of PGMs reported by various studies, such as Maynard et al.,[24] differed between different work areas and between different activities. Personal exposure to soluble PGMs was also reported to exceed the OEL during nonroutine activities.[68] It is recommended that a variety of work areas and nonroutine tasks be included in exposure assessments as they can often be overlooked when assessing exposure.

(iii) It was noted that research papers reported the exposure monitoring results in a variety of ways, depending on the main focus of the study (i.e., medical surveillance or degree of exposure). To easily compare exposure monitoring results with other studies, it is recommended that authors report the number of measurements collected, minimum, maximum and arithmetic or geometric mean concentrations of measurements collected in specific work areas (e.g., n = 13; min = 0.004 $\mu g/m^3$; max = 11.605 $\mu g/m^3$; arithmetic mean = 1.704 $\mu g/m^3$; geometric mean = 0.387 $\mu g/m^3$; area = bagging department of a precious metals refinery).

(iv) It is recommended that the chemical form (metallic or soluble) of the particular PGM measured is clearly stated as it will have a considerable effect on the manner in which the results are interpreted.

(v) Respiratory sensitization is the most significant adverse health effect following respiratory exposure to soluble PGM compounds,[19] yet only some countries/organizations (United Kingdom, South Africa, Sweden, Australia, Germany, British Colombia, and Japan) have classified soluble Pt compounds as respiratory or skin sensitizers.[71−73,75−78] Only Germany has classified Pd(II) compounds as skin sensitizers, and only Japan has classified Rh compounds as possible skin sensitizers.[71,78] It is recommended that more countries and organizations classify soluble PGM compounds (especially soluble Pt) as respiratory or skin sensitizers to emphasize of the risk involved in working with these compounds.

15. CONCLUSION

Many studies have reported occupational exposure to Pt but studies reporting occupational exposure to Pd, Rh, and Ir are scarce since these PGMs are not as potent allergens as Pt. The highest concentrations of airborne Pt have been measured in precious metals refineries where personal exposure to soluble Pt frequently exceeded the TWA-OEL of 2 $\mu g/m^3$. It is clear that the risk of becoming sensitized to soluble Pt is associated with the degree of exposure experienced by workers, and this review indicated that occupational respiratory exposure to PGMs is dependent on the type of industry where exposure takes place, the chemical form (soluble or insoluble) of the PGMs present in the workroom air, and the tasks performed by workers in the specific work areas.

Furthermore, area measurements should not be used instead of personal measurements to indicate the PGM exposure experienced by workers and a variety of areas and tasks (routine and nonroutine) should be monitored to identify the scenarios where the risk for sensitization is the highest. Also, consistent reporting methodologies are needed as it will allow for meaningful comparisons to be made between various studies. It is also important that the chemical form of the PGM that was measured be reported since it will have a substantial effect on the manner in which the results are interpreted.

There are limitations to the legislation regarding occupational exposure to PGMs with many publications arguing that the current OEL (2 $\mu g/m^3$), which has been in use since 1970, is not protective of worker health and that sensitization can occur at exposure below this level. In addition, only a few countries/organizations have classified soluble PGM compounds as respiratory or skin sensitizers although they are known to cause sensitization.

Finally, it was noted that inhalation should not be the only route of exposure considered when assessing occupational exposure to PGMs. Pt, Pd, Rh, and Ir have been shown to cause adverse dermal health effects, and *in vitro* studies have shown that Pt, Pd (nanoparticles), and Rh permeate through intact human skin.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AAS-GF, graphite furnace atomic absorption spectrometry; ACGIH, American Conference of Governmental Industrial Hygienists; DECOS, Dutch Expert Committee on Occupational Standards; HSE, health and safety executive; ICP-AES, inductively coupled plasma-atomic emission spectroscopy; ICP-MS, inductively coupled plasma mass spectrometry; Ir, iridium; IgE, immunoglobulin E; IOM, Institute for Occupational Medicine; IPA, International Platinum Group Metals Association; JSOH, Japan Society for Occupational Health; LOD, limit of detection; MCE, mixed cellulose ester; MDHS, methods for the determination of hazardous substances; NIOSH, National Institute for Occupational Safety and Health; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration; Os, osmium; Pd, palladium; $PdCl_2$, palladium chloride; PEL, permissible exposure limit; PGM, platinum group metal; Pt, platinum; PVC, poly vinyl chloride; Rh, rhodium; Ru, ruthenium; TPC, tetra-ammine platinum trichloride; TLV, threshold limit value; TWA, time weighted average; WEL, workplace exposure limit; WHO, World Health Organization

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CHAPTER 4: ARTICLE II

Linde SJL, Franken A, du Plessis JL. (2017) Urinary excretion of platinum from South African precious metals refinery workers. Submitted to the journal *Occupational and Environmental Medicine* to be considered for publication.

4.1 Background

Most precious metals refineries only conduct respiratory exposure monitoring and, therefore, do not take into account exposure via the skin or ingestion. It was decided to conduct biological monitoring at two South African precious metals refineries to assess the platinum body burden of precious metals refinery workers. Urinary platinum excretion has previously been used to assess the platinum body burden of workers exposed to platinum compounds in precious metals refineries and automotive catalyst production plants. This is the first article to report the urinary platinum excretion of workers in South African precious metals refineries.

4.2 Instructions to authors (excerpt)

Occupational and Environmental Medicine is an international peer reviewed journal covering current developments in occupational and environmental health worldwide. *Occupational and Environmental Medicine* publishes high-quality research relating to the full range of chemical, physical, ergonomic, biological and psychosocial hazards in the workplace and to environmental contaminants and their health effects. The journal welcomes research aimed at improving the evidence-based policy and practice of occupational and environmental research; including the development and application of novel biological and statistical techniques in addition to evaluation of interventions in controlling occupational and environmental risks.

Manuscript format: The manuscript should be presented in the following order: Title page; abstract, main text separated under appropriate headings and subheadings; acknowledgments, competing Interests, funding and all other required statements and reference list.
Authors should also provide key messages under the following headings:

- What is already known about this subject?
- What are the new findings?
- How might this impact on policy or clinical practice in the foreseeable future?

Tables: Tables should be placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order.

Figures/illustrations: All images must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.
Appendices should be uploaded using the File Designation “Supplementary File” and cited in the main text.

Language: Please note that during this article, the abbreviation for platinum (Pt) is used in the text since this is the format in which the article was submitted to the journal.

References: References must be numbered sequentially as they appear in the text. References cited in figures or tables (or in their legends and footnotes) should appear at the end of the reference list to avoid re-numbering if tables and figures are moved around at peer review/proof stage. Reference numbers in the text should be inserted immediately after punctuation (with no word spacing)—for example,[6] not [6].
Where more than one reference is cited, these should be separated by a comma, for example,[1, 4, 39]. For sequences of consecutive numbers, give the first and last number of the sequence separated by a hyphen, for example,[22-25].
References must be numbered consecutively in the order in which they are mentioned in the text. The following guidelines should be used:
List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add ‘et al.’ (The exception is the Journal of Medical Genetics, which lists all authors). Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

Reference examples:
13 Koziol-Mclain J, Brand D, Morgan D, *et al.* Measuring injury risk factors: question reliability in a statewide sample. Inj Prev 2000;6:148–50.

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates. Washington, DC: National Academy of Sciences 1978:95–139.

15 Howland J. Preventing Automobile Injury: New Findings From Evaluative Research. Dover, MA: Auburn House Publishing Company 1988:163–96.

Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The “date accessed” can be later than the acceptance date of the paper, and it can be just the month accessed.

Morse SS. Factors in the emergency of infectious diseases. Emerg Infect Dis 1995 Jan-Mar;1(1). www.cdc.gov/nciod/EID/vol1no1/morse.htm (accessed 5 Jun 1998).

4.3 Urinary excretion of platinum from South African precious metals refinery workers

Abstract

Background Urinary platinum (Pt) excretion is a reliable biomarker for occupational Pt exposure and has been previously reported for precious metals refinery workers in the United Kingdom and Europe but not for South Africa, the world's largest producer of Pt.

Objective This study aimed to quantify the urinary Pt excretion of South African precious metals refinery workers.

Methods Spot urine samples were collected from 40 workers (directly and indirectly exposed to Pt) at two South African precious metals refineries on three consecutive mornings prior to their shifts. Urine samples were analysed for Pt using inductively coupled plasma-mass spectrometry and were corrected for creatinine content.

Results The urinary Pt excretion of workers did not differ significantly between sampling days. Urinary Pt excretions ranged from <0.1 to 3.0 µg Pt/g creatinine with a geometric mean of 0.21 µg Pt/g creatinine (0.17-0.26 µg Pt/g creatinine, 95% confidence interval]). The work area ($p=0.0006$; $\eta^2=0.567$) and the number of years workers were employed ($p=0.003$; $\eta^2=0.261$) influenced their urinary Pt excretion according to effect size analyses. Directly exposed workers had significantly higher urinary Pt excretion compared to indirectly exposed workers ($p=0.007$).

Conclusion The urinary Pt excretion of South African precious metals refinery workers reported in this study is comparable to that of seven other studies conducted in precious metals refineries and automotive catalyst plants in the United Kingdom and Europe. The Pt body burden of workers are predominantly determined by their work area, years of employment and whether they are directly or indirectly exposed to Pt.

Key words: Biological monitoring; occupational exposure; spot urine samples.

1. **What is already known about this subject?**

- Urinary platinum (Pt) excretions of precious metals refinery workers have been reported for Europe, the United Kingdom and the United States of America but not for South Africa, the largest producer of Pt in the world.

2. **What are the new findings?**

- This is the first paper to report the urinary Pt excretions of South African precious metals refinery workers. Their urinary Pt excretions are comparable to concentrations reported for precious metals refinery workers in the other countries.

- The urinary Pt excretions of workers were determined by their work area, years of employment and whether they had direct contact with Pt compounds or not.

3. **How might this impact on policy or clinical practice in the foreseeable future?**

- Urinary Pt excretions can be used for risk assessment and to indicate increased exposure or Pt body burden in South African precious metals refineries.

Introduction

Allergic reactions of the airways and skin resulting from occupational exposure to soluble platinum (Pt) compounds are well known and have been frequently reported in precious metals refinery workers.[1-5] Cases of refinery workers suffering from asthmatic symptoms caused by soluble Pt compounds were first reported in British refineries in 1945 where the symptoms were linked with respiratory exposure.[1] Since then, a number of investigations have associated sensitisation to soluble Pt with the degree of exposure to soluble Pt compounds experienced by workers[2, 5, 6,] and increased urinary Pt excretions have been observed in workers who work in high exposure areas.[7] Biological monitoring techniques such as the assessment of urinary Pt excretion can, therefore, be used to assess the exposure experienced by workers.[8] In order to accurately assess exposure to a chemical substance through biological monitoring, the kinetics of the chemical in the human body needs to be understood since it affects the biological matrix which is used and the timing of the sample.[9]

The excretion of Pt is slow.[10, 11] Schierl *et al.*[11] exposed two human volunteers to soluble Pt dust through the handling of dry ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$] powder for four hours. The urinary Pt excretion from these volunteers reached a maximum approximately 10 hours following cessation of exposure and followed a bi-phasic exponential decay pattern which corresponded to a first half-life of 50 hours [36-66 hours, 95% confidence interval (CI)] and a second half-life of 24 days (18-33 days, 95% CI). Even 166 days after exposure had ceased the excretion of Pt via the urine was still above the baseline concentrations. Schierl *et al.*[11] also reported that urinary Pt excretion from employees who had not been exposed to Pt for several years were still 25-fold higher than that of non-exposed subjects and Weber *et al.*[10] reported no decrease in urinary Pt excretion from automotive catalyst production workers following two weeks of vacation. It was suggested that a long term Pt reservoir could form in the body from where Pt may be gradually released for several years after exposure ends.[11]

Small amounts of Pt have been reported to permeate through intact human skin during *in vitro* permeation studies.[12, 13] During these studies, most of the Pt was retained inside the skin leading the authors to state that a Pt reservoir may form inside the skin from where Pt could be gradually released. Therefore, the skin may possibly serve as an exposure route for Pt.

Urine has been identified as a reliable biological matrix for use when performing biological monitoring of Pt exposure and has been used in several studies in occupational settings.[7, 8, 11, 14, 15] The concentration of Pt in urine may be used to distinguish between workers who work in high exposure areas and those who work in areas with lower exposure.[7, 16] Cristaudo *et al.*[8] reported Pt concentrations in workplace air and in biological samples (urine, blood and hair) of catalyst production and metal recycling workers. They observed a very strong

positive correlation between Pt concentrations in the workplace air and Pt concentrations in the urine of workers and reported that urine is a reliable biomarker of short term exposure to Pt.

In addition to refinery and catalyst production workers, urinary Pt excretion has been measured in workers who were occupationally exposed to Pt in roadside dust, hospital workers who prepared the anti-neoplastic drug, cisplatin, and dental technicians who treated dental alloys with Pt.[17-21] However, these concentrations did not compare to the high concentrations reported for refineries and automotive catalyst production plants.[4]

Tighter restrictions on motor vehicle emissions have led to the increased production of automotive catalysts and an increase in the demand for Pt.[8, 22] This has led to an increased number of workers potentially being exposed to Pt compounds. Although urinary Pt excretions of workers have been reported for precious metals refineries in Europe and the United Kingdom, no concentrations have been reported for South Africa, the largest supplier of Pt in the world.[11, 15, 22] Therefore, the main aim of this study was to quantify the urinary Pt excretion of South African precious metals refinery workers in order to compare it with the published literature. Additionally, since previous studies have demonstrated that urinary Pt excretions can be used to identify workers who experienced increased exposure to Pt,[7] this study also aimed to distinguish between the urinary Pt excretions of different groups of workers (e.g. workers from various work areas).

Methods

Study population

Forty workers (32 men and eight women; 31 African and nine Caucasian) from two South African precious metals refineries were included in the study. Only workers employed at the refineries for longer than one year were included. The workers were aged between 22 and 56 years (mean = 34.6 ± 7.9 years) and the number of years which they were employed at the refinery was between one and 27 years (mean 7.7 ± 6.3 years). As a control group, 10 persons (7 men and three women; 2 African and 8 Caucasian) aged between 25 and 62 (mean = 36.5), who lived >100 km from the nearest Pt industry, were included. For the purpose of this study the term *race* is used to define specific population groups based on genetic similarities, namely skin colour and physical features.[23] The participants all received information regarding the details of the study prior to the start and provided written consent to participate in the study. Ethical approval for the study was obtained from the Health Research Ethics Committee of the North-West University (NWU-00128-14-A1).

Workers with various job titles, working in different work areas within the refineries were included. These work areas included: concentrate handling, PGM separation, crushing and ignition, precious metals, other precious metals, other production activities, other non-production activities, security, and the health clinic. A detailed description of the workplace is provided in the supplementary material. Prior to statistical analysis, workers were grouped into either a direct or an indirect exposure group. Workers in the direct exposure group were directly involved in production activities and came into direct contact with Pt compounds (concentrate handling, separation, precious metals, other precious metals and maintenance workers). Workers from the indirect exposure group were not directly involved in process activities but still came in contact with Pt compounds though indirect pathways while performing laundry, security, laboratory and health clinic activities.

Collection and analysis of urinary platinum

Schierl *et al.*[11] reported that the urinary Pt excretion of volunteers reached the maximum approximately 10 hours after exposure. Therefore spot urine samples were collected in the morning, approximately 16 hours after the cessation of the previous shift's exposure. Spot urine samples were therefore, collected on three consecutive mornings, prior to the start of the shift and represented the maximum urinary platinum excretion following the previous day's exposure. No "baseline" or "before exposure" urine samples could be obtained and the three spot urine samples represented the urinary Pt excretion of workers over a 48 hour period during normal working conditions. Whole urine samples were collected at the refineries' health clinics, after which a representative 20 ml of the sample was decanted into a suitable high-density polyethylene bottle (Ampath, South Africa). Urine samples were frozen following collection and analysed by Ampath Laboratories (South Africa) using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). The limit of detection (LOD) for Pt in urine was 0.1 µg/l.

Statistical data analysis

Statistical analysis was carried out using Statistica version 13.2 (Statsoft Inc., Palo Alto, California) and figures were created using GraphPad Prism version 6.0 (GrapPad Software, San Diego, California). Results for measurements that were below the LOD for the analytical method were substituted using β-substitution, a substitution method recommended by Ganser and Hewett.[24] Urinary Pt concentrations were not normally distributed and were, therefore, log-transformed prior to statistical analysis. All results were expressed as µg Pt/g creatinine, in order to account for the degree of dilution of the urine samples, by dividing the mass of Pt (µg) by mass of creatinine (g) in the urine sample. However, since the majority of published studies only reported concentrations of urinary Pt excretion in µg Pt/l, concentrations were also expressed in µg Pt/l, in order to facilitate comparison between the present study and published

literature. Pearson correlation analyses were used to perform correlations between the raw (µg Pt/l) and the creatinine corrected Pt concentrations. Repeated measures analyses of variance (ANOVAs) were used to compare the urinary Pt concentrations of the three sampling days. The variation in urinary Pt excretion between different groups of was compared for statistical significance using either paired Student's t-tests (sex, race and direct or indirect exposure groups) or analyses of covariance (ANCOVA) (age, year employed and work areas). The ANCOVA with a Tukey post-hoc test compared the urinary Pt excretion of workers in different work areas while including their years of employment at the refineries as covariates. Effect sizes, through partial eta-squared (η^2) values, were used to indicate the practical significance that factors such as years of employment and work area had on the urinary excretion of Pt.[25] For example a partial eta-squared value of 0.5 indicated that the specific variable explained 50% of the variation in urinary Pt excretion. Analyses with a $p \leq 0.05$ were considered to be statistically significant.

Results

Figure 1 illustrates the urinary Pt excretions from the first, second and third spot urine samples collected from all of the participants at the two refineries. A geometric mean (GM) urinary Pt excretion of 0.19 µg Pt/g creatinine (0.13-0.29 µg Pt/g creatinine, 95% CI) was measured for day one, 0.23 µg Pt/g creatinine (0.16-0.35 µg Pt/g creatinine, 95% CI) for day two and 0.21 µg Pt/g creatinine (0.14-0.31 µg Pt/g creatinine, 95% CI) for day three. A repeated measures ANOVA did not show statistically significant differences between the urinary Pt excretions on the three consecutive days of sampling (p=0.262).

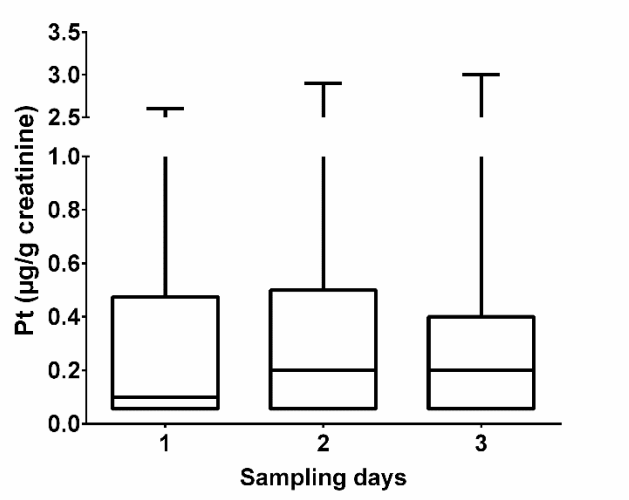

Figure 1: Summary of the urinary Pt concentrations (µg Pt/g creatinine) of the first, second and third spot urine samples. The line in the middle of the box indicates the median concentration. The box extends from the 25th to the 75th percentiles while the upper and lower limits indicate the maximum and minimum values, respectively.

The urinary Pt excretions from all of the refinery workers (n=40) who participated in the study are summarised in Table 1 where the workers were divided into groups according to work areas, exposure categories (direct or indirect exposure), sex, race, age groups and years of employment. The urinary Pt excretion concentrations in Table 1 are expressed in µg Pt/g creatinine as well as µg Pt/l, and since the data was not normally distributed, the GM and the GM's 95% CIs were calculated. Pearson correlations showed a very strong positive correlation ($r=0.948$) ($p<0.001$) between the raw and the creatinine corrected Pt concentrations. A GM urinary Pt excretion of 0.21 µg Pt/g creatinine (0.17-0.26 µg Pt/g creatinine, 95% CI) was measured for the total group of workers and the concentrations ranged from < 0.10 to 3.00 µg Pt/g creatinine. The urinary Pt excretions from the ten participants in the control group were all below the LOD of 0.1 µg/l.

The highest GM urinary Pt excretion was observed in the concentrate handling area [0.58 µg Pt/g creatinine (0.34-0.98 µg Pt/g creatinine, 95% CI)] followed by the precious metals area [0.53 µg Pt/g creatinine (0.29-0.97 µg Pt/g creatinine, 95% CI)] and the crushing and ignition area [0.47 µg Pt/g creatinine (0.27-0.83 µg Pt/g creatinine, 95% CI)]. The lowest GM urinary Pt concentrations were found in the other precious metals area [0.07 µg Pt/g creatinine (0.05-0.11 µg Pt/g creatinine, 95% CI)] and in the group of workers performing other production activities [0.07 µg Pt/g creatinine (0.05-0.09 µg Pt/g creatinine, 95% CI)].

Figure 2 illustrates the urinary Pt excretions as measured in various work areas as well as the areas where workers were directly or indirectly exposed to Pt. Workers who were directly exposed to Pt had statistically significant higher urinary Pt excretions compared to workers who were indirectly exposed to Pt ($p=0.007$). The influence that years of employment had on the urinary Pt excretions of workers was also investigated and was included as covariate in the ANCOVA. The area where workers worked had the largest effect on their urinary Pt excretion ($p=0.0006$; $\eta^2=0.567$) while their years of employment also had a statistically significant effect on their urinary Pt excretion ($p=0.003$; $\eta^2=0.261$). Therefore, 57% of the variation in workers' urinary Pt excretion was explained by their work area while 26% was due to the years which they were employed at the refinery. The ANCOVA with a Tukey post-hoc test identified statistically significant differences between the urinary Pt excretions of workers from different work areas [Table 1 and Figure 2 (a-g)].

Table 1: Concentrations of Pt measured in urine of precious metals refinery workers

		n (%)	Years employed		(µg Pt/g creatinine)		(µg Pt/l)		n < LOD
			AM	Range	GM	95% CI	GM	95% CI	
Work area	Concentrate handling	18 (15)	8.67	1-26	0.58[a,b,c]	0.34-0.98	0.83	0.47-1.50	1
	PGM separation	15 (13)	8.00	1-24	0.26	0.16-0.45	0.48	0.28-0.82	0
	Crushing and ignition	12 (10)	5.00	4-6	0.47	0.27-0.83	0.72	0.35-1.50	0
	Precious metals	18 (15)	8.83	3-17	0.53[d,e,f]	0.29-0.97	0.96	0.53-1.80	0
	Other Precious metals	12 (10)	5.50	3-8	0.07[a,d]	0.049-0.11	0.07	0.049-0.096	9
	Other production activities	8 (7)	7.33	3-12	0.07[b,e]	0.054-0.089	0.12	0.073-0.20	5
	Other non-production activities	15 (13)	8.60	2-13	0.10[c,f]	0.062-0.17	0.10	0.057-0.16	9
	Security	11 (9)	6.25	3-9	0.11	0.077-0.15	0.11	0.081-0.16	2
	Health clinic	9 (8)	10.67	3-15	0.09	0.046-0.18	0.08	0.044-0.13	6
Exposure category	Direct exposure	89 (75)	7.80	1-27	0.29[g]	0.22-0.37	0.42	0.31-0.56	16
	Indirect exposure	29 (25)	7.50	3-15	0.09[g]	0.07-0.11	0.08	0.06-0.10	16
Sex	Male	95 (81)	8.00	1-27	0.27	0.21-0.35	0.39	0.29-0.51	18
	Female	23 (19)	6.63	4-14	0.08	0.06-0.10	0.07	0.06-0.09	14
Race	Caucasian	26 (22)	9.11	5-24	0.35	0.19-0.64	0.53	0.26-1.08	5
	African	92 (78)	7.32	1-27	0.18	0.15-0.23	0.23	0.18-0.30	26
Age	20-29	26 (22)	4.56	1-8	0.26	0.15-0.43	0.38	0.21-0.71	6
	30-39	66 (56)	6.00	1-14	0.18	0.13-0.23	0.22	0.16-0.31	18
	40-49	20 (17)	14.14	3-27	0.26	0.15-0.48	0.33	0.16-0.68	5
	≥50	6 (5)	19.00	12-26	0.33	0.04-2.60	0.53	0.13-2.20	3
Years employed	1-4	44 (37)	2.93	1-4	0.14	0.11-0.18	0.17	0.12-0.22	14
	5-10	44 (37)	6.53	5-9	0.24	0.16-0.36	0.38	0.24-0.60	8
	10-19	21 (18)	12.86	12-15	0.16	0.09-0.29	0.20	0.10-0.38	10
	≥20	9 (8)	25.67	24-27	1.50	1.20-1.80	1.90	0.30-2.90	0
Total		118 (100)	7.73	1-27	0.21	0.17-0.26	0.28	0.22-0.36	32

n – Number of urine spot tests; % – percentage of the total number of samples; LOD – Limit of Detection (0.1 µg/l); Values which were below the limit of detection were substituted by means of beta substitution; AM – Arithmetic mean; GM – Geometric mean; CI – Confidence interval; [a-g] indicates statistical significant differences in urinary platinum excretion (µg Pt/g creatinine) according to ANCOVA with Tukey post-hoc tests.

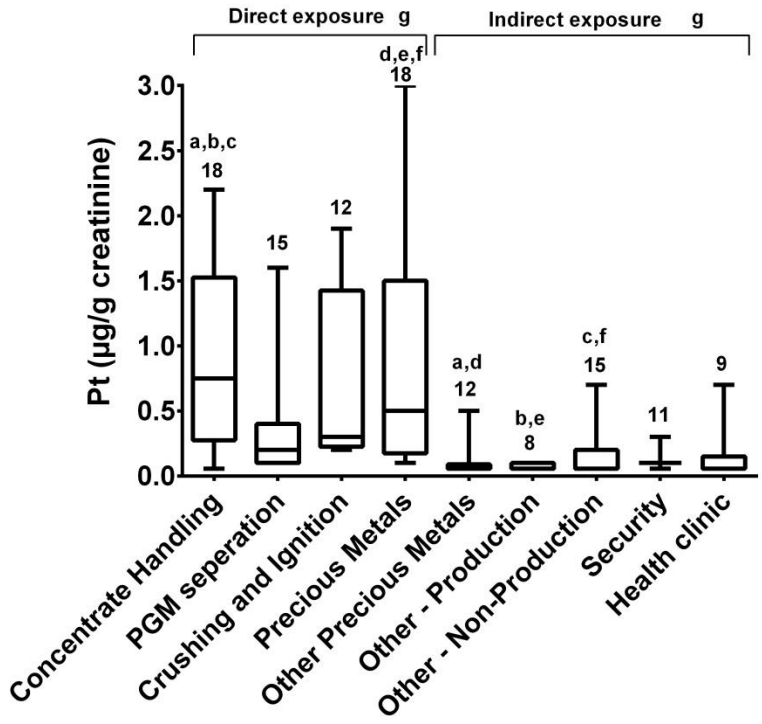

Figure 2: Summary of urinary Pt excretions (µg Pt/g creatinine) of workers in various work areas of the refineries. The line in the middle of the box indicates the median concentration. The box extends from the 25th to the 75th percentiles while the upper and lower limits indicate the maximum and minimum values, respectively. The number of samples (n) collected from each work area is indicated above each plot. The letters above the graphs indicate statistically significant differences between the urinary Pt excretions from different work areas as determined with the ANCOVA and Tukey post-hoc test. The brackets above the figure indicate the areas where workers were directly or indirectly exposed to Pt.

Workers were grouped into categories according to their sex, race, age and the number of years which they were employed at the refinery. A statistical significant difference was observed between the urinary Pt excretions of men compared to women (p=0.007), but no statistical differences were observed between race (Africans and Caucasians) (p=0.206) or between the various age groups (p=0.705). However, after including the work areas as covariate, the differences between sexes was no longer statistically significant (p=0.339).

Discussion

This study aimed to quantify the urinary Pt excretion of South African precious metals refinery workers over three consecutive work days. Additionally, this study aimed to distinguish between the urinary Pt excretions of different groups of workers in order to identify work areas which

pose increased risks to the health of workers. Although the urinary Pt excretion of precious metals refinery and automotive catalyst production workers in Europe and the United Kingdom have been reported,[8, 11, 15] this is the first study to report the urinary Pt excretion of precious metals refinery workers in South Africa, the world's largest supplier of Pt.[22]

Schaller *et al.*[14] determined that urine can be used to estimate elevated Pt intake and other investigations conducted in automotive catalyst production plants reported that urinary Pt is an efficient biomarker for occupational biological monitoring and that urinary Pt can be used as a reliable marker for short-term occupational exposure.[7, 8] The use of urinary Pt excretion in occupational monitoring usually involves the collection of spot urine samples,[7, 8, 11, 14, 15] which is advantageous, since spot urine samples are non-invasive and easy to collect.[26] However, spot samples only provide a brief snapshot of the concentration of a chemical within an individual at a specific point in time and do not necessarily represent the internal concentration over longer time periods. This may lead to misinterpretation or misuse of results which can lead to the misclassification of the degree of exposure experienced by workers.[26-28] According to Smolders *et al.*[28], the elimination half-life of the chemical in question, the pattern and intensity of exposure and the sampling parameters are factors which should be understood when collecting spot urine samples since they can influence the representativeness of the results. Especially the relationship between the chemical's elimination half-life and the exposure interval is of particular importance.[27] The variation in the representativeness of the spot urine samples is the lowest when the chemical's elimination half-life is long and the exposure to the chemical is frequent, and is the greatest when the chemical's elimination half-life is short and the exposure to the chemical is infrequent.[27, 28] The elimination half-life of Pt is long[11] and refinery workers are exposed to Pt-compounds on a daily basis. Figure 1 showed that there was no significant difference between the three sampling days and that the spot urine samples collected during the study did not have a high degree of variability. This corresponds to Schierl *et al.*[29] who reported very small intra-individual variability of urinary Pt concentrations during their study and revealed that single spot urine samples could be used instead of 24 hour samples to investigate the urinary Pt excretion of patients who were treated with cis-platin during chemotherapy. Since the urinary Pt excretion of workers did not differ significantly between sampling days, spot urine samples could be used to determine which workers had an increased urinary Pt excretion or Pt body burden, compared to others.

A creatinine correction was used to adjust for the dilution of the spot urine samples. In a study on the variability of urinary metal biomarkers, Smolders *et al.*[28] reported that the creatinine

correction correlated better to the calculated excretion rate of the metals than the raw uncorrected data. Therefore, although there was a high correlation between raw and the creatinine corrected data during this study, the creatinine corrected data should be used when reporting urinary Pt excretion.

Previous studies have associated increased urinary Pt excretion with work areas where the airborne Pt was known to be high.[8, 11, 15] It was observed during this study (Figure 2) that the area of work had the greatest influence on the urinary Pt excretions of workers and that the mean urinary Pt excretions of workers who were directly exposed to Pt during production activities were significantly higher than that of workers who came into indirect contact with Pt compounds during non-production activities. Figure 2 also shows that the urinary Pt excretion measured in the concentrate handling area, where PGM-containing material was received, sieved and concentrated, were significantly higher than the urinary Pt excretion measured in areas where workers handled other PGMs [rhodium (Rh), iridium (Ir), ruthenium (Ru) and osmium (Os)] ($p=0.021$), areas where workers performed other production activities (laboratory, melting and packaging) ($p=0.020$) as well as areas where workers performed other non-production activities (laundry, laboratory and maintenance) ($p=0.032$). The urinary Pt excretion measured in the precious metals area, where Pt and palladium (Pd) salts were handled, were also significantly higher than the results from areas where workers worked with other precious metals ($p=0.027$) and where workers performed other production ($p=0.026$) and non-production ($p=0.043$) activities.

A significant difference was observed between the urinary Pt excretions of men compared to women. However, only two of the eight women worked in production areas (other precious metals area) with the other six performing in non-production activities (indirect exposure). Subsequently these significant differences became non-significant with the inclusion of work area as a covariate. This suggests that the difference between the urinary Pt excretions of men and women was caused by the differences in work area rather than sex related differences.

The urinary Pt excretion of the refinery workers were influenced by their work areas as well as the number of years which they were employed at the refineries. Schierl *et al.*[11] measured elevated urinary Pt excretions in workers two to six years after their previous exposure episodes and suggested that, following exposure, a reservoir of Pt could form in the body similar to that found in patients following treatment with cisplatin.[29] It might be possible that working in high exposure areas within the refinery for many years increases the Pt reservoir in the body which

could then be gradually released into the systemic circulation and lead to increased urinary Pt excretion.

The urinary Pt excretions observed during this study (< 0.10 to 3.00 µg Pt/g creatinine or < 0.10 to 5.40 µg Pt/l) is comparable to results reported by other studies conducted in precious metals refineries and automotive catalyst production plants. Johnson *et al.*[30] and Farago *et al.*[15] reported urinary Pt excretions for precious metals refinery workers of between < 0.1 and 2.58 µg Pt/l and between 0.21 and 1.18 µg Pt/g creatinine, respectively. Schierl *et al.*[11] reported urinary Pt excretions of between 0.016 and 6.27 µg Pt/g creatinine in a refinery and catalyst production company where spot urine samples were collected at the end of the shift and on the morning following exposure. Weber *et al.*[10] and Schaller *et al.*[14] reported urinary Pt excretions for automotive catalyst production workers of between 0.01 and 2.90 µg Pt/l and between 0.02 and 9.20 µg Pt/l, respectively. More recently, Cristaudo *et al*.[8] reported mean urinary Pt excretions in an automotive catalyst production plant ranging from 0.10 µg Pt/l in the administrative area to 1.86 µg Pt/l in the coating area.

Conclusion

This was the first study to report quantifiable concentrations of Pt in the urine of South African precious metals refinery workers. The urinary Pt excretion of workers did not vary statistically between the different sampling days. This was consistent with other metal biological monitoring studies which stated that a long elimination half-life of a particular metal and frequent exposure to it will cause its concentration in spot urine samples to have a low degree of variability.

Similar to previous studies, this study reported significant differences between the urinary Pt excretion of workers from various work areas within the refineries. Significantly higher urinary Pt excretion was observed in areas where workers were directly exposed to Pt compounds during production activities compared to areas where they were indirectly exposed during non-production activities. The urinary Pt excretion of workers can, therefore, be used to differentiate between workers who are directly or indirectly exposed to Pt or workers who work in high or low exposure areas. Additionally, the number of years of employment at the refineries also influenced their urinary Pt excretion.

The urinary Pt excretion of South African precious metals refinery workers observed during this study was comparable to seven other studies conducted in precious metals refineries and automotive catalyst production plants in Europe and the United Kingdom.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore the NRF does not accept any liability in regards thereto. The authors declare no competing financial interest.

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Supplementary material

Workplace description

Work areas included in this study were the concentrate handling, platinum group metals (PGM) separation, crushing and ignition, precious metals, other precious metals, other production activities, other non-production activities, security, and the health clinic. In the concentrate handling area, the platinum group metals (PGMs) concentrate was received, sieved and concentrated further after which the concentrate was loaded into the reactors of the PGM separation areas where it was dissolved using acids. In the PGM separation areas, the various precious metals were separated from the concentrate mixture and sent to the purification areas to be precipitated and purified. Platinum (Pt) and palladium (Pd) compounds were purified in the precious metals area while rhodium (Rh), iridium (Ir), ruthenium (Ru) and osmium (Os) compounds were purified in the other precious metals area. The metals were precipitated from the solution in the form of chlorinated salts and removed using filter presses and glove boxes. Next, the chlorinated precious metals salts were ignited in the ignition areas to form a metal sponge and crushed into specific sizes in the crushing areas. The metal sponge or crushed particles were then either melted into bars or packaged for shipping. Other production activities included melting of Pt and packaging of PGMs while other non-production activities included handling laundry, laboratory work, and maintenance. Workers who performed security activities in various work areas and workers from the health clinic were also included in the study.

CHAPTER 5: ARTICLE III

Linde SJL, Franken A, du Plessis JL. (2017) Biological monitoring of platinum following dermal and respiratory exposure to soluble platinum at South African precious metals refineries. Submitted to the journal *Contact Dermatitis* to be considered for publication.

5.1 Background

Soluble platinum has recently been shown to permeate through the skin and it has been postulated that dermal exposure to soluble platinum may contribute to sensitisation, especially when airborne soluble platinum concentrations are low. In order to shed more light on the relationship between dermal exposure and platinum body burden, precious metals refinery workers' dermal and respiratory exposure to soluble platinum as well as their urinary platinum excretion was assessed concurrently. This is the first article to report dermal exposure to soluble platinum in any occupational setting.

5.2 Instructions to authors (excerpt)

Contact Dermatitis is designed primarily as a journal for clinicians who are interested in various aspects of environmental dermatitis. This includes both allergic and irritant (toxic) types of contact dermatitis, occupational (industrial) dermatitis and consumers' dermatitis from such products as cosmetics and toiletries. The journal aims at promoting and maintaining communication among dermatologists, industrial physicians, allergists and clinical immunologists, as well as chemists and research workers involved in industry and the production of consumer goods. Papers are invited on clinical observations, diagnosis and methods of investigation of patients, therapeutic measures, organisation and legislation relating to the control of occupational and consumers' contact dermatitis, preventive measures and educational advice. *Contact Dermatitis* accepts original articles, review articles, 'Contact Points', see below, contributions addressing 'Education and Debates' and letters to the editor.

Manuscript format: Manuscripts should include introduction; methods; results and discussion sections. A structured abstract and 3-8 key words should also be provided. Original papers and review articles should, in most cases, not exceed 8 printed pages (approx. 700 words per printed page).

Tables: Tables should be numbered consecutively with Arabic numerals. Type each table on a separate sheet, with titles and footnotes making them self-explanatory.

Figures: Figures should clarify the text and their numbers be kept to a minimum. Figure legends should allow interpretation of the figures without reference to the main text; they should appear according to their order of appearance in the text.

References: Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in parentheses). All publications cited, and only these, must be listed at the end of the paper.
References should follow the following style examples:

1. Giwercman C, Lerbaek A, Bisgaard H, Menné T. Classification of atopic hand eczema and the filaggrin mutations. *Contact Dermatitis* 2008: **59**: 257-260.

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5.3 Biological monitoring of platinum following dermal and respiratory exposure to soluble platinum at South African precious metal refineries

Abstract

Background. Although occupational exposure to soluble platinum is associated with adverse respiratory and dermal effects, dermal exposure to soluble platinum and its effect on the platinum body burden has not yet been investigated.

Objectives. To examine the relationship between dermal and respiratory exposure to soluble platinum and urinary platinum excretion at two South African precious metals refineries.

Methods. The dermal and respiratory exposure to soluble platinum as well as the urinary platinum excretion of forty precious metals refinery workers was assessed simultaneously using Ghostwipes™, Methods for the Determination of Hazardous Substances method 46/2 and spot urine tests, respectively.

Results. The geometric mean for dermal exposure to soluble platinum on four anatomical positions was 0.008 µg/cm^2 [95% confidence interval (CI): 0.005-0.013 µg/cm^2], while the geometric mean for respiratory exposure was 0.301 µg/m^3 (95%CI: 0.151-0.601 µg/m^3) and the geometric mean for urinary platinum excretion was 0.212 µg/g creatinine (95%CI: 0.169-0.265 µg/g creatinine). Partial correlations identified significant positive correlations between dermal exposure, respiratory exposure and urinary platinum excretion (r = 0.580 to 0.754).

Conclusions. Dermal and respiratory exposures to soluble platinum were both positively correlated with urinary platinum excretion and both exposure routes should be considered when investigating occupational exposure to platinum.

Key words:
Urinary platinum; platinum group metals; skin exposure; platinum body burden; Ghostwipes™; MDHS 46/2.

Introduction

Occupational exposure to soluble platinum compounds occurs during the mining and refining of platinum as well as during the manufacturing of platinum products. The highest levels of respiratory exposure to soluble platinum have been measured in precious metals refineries (1, 2). South Africa is the world's largest producer of platinum (3) and respiratory exposure to soluble platinum at South African precious metals refineries has been reported to frequently exceed the occupational exposure limit (OEL), especially in production areas (4–7). Several studies have associated the intensity of respiratory exposure to soluble platinum with the development of platinum salt sensitisation, which is the most prominent adverse health effect associated with soluble platinum exposure (4, 7, 8).

The majority of soluble platinum salts are powerful sensitisers, while the metallic form of platinum is considered to be non-allergenic (9). The allergy symptoms observed in workers sensitised to soluble platinum indicate a type I reaction mediated by Immunoglobulin (Ig) E (7). Following sensitisation, workers are usually removed from areas where they could be exposed further. However this does not exclude the possibility of developing chronic asthma later in life (10). Occupational exposure to soluble platinum is associated with several adverse dermal health effects such as dermatitis, eczema and urticaria, as well as adverse respiratory effects such as asthma, rhinitis and shortness of breath (11–14). Soluble platinum has been classified as a respiratory sensitiser by the South African Department of Labour as well as in other countries such as the United Kingdom (15, 16). In Germany and Japan, soluble platinum is classified as respiratory and skin sensitisers to indicate that it may cause allergic reactions of the skin and the airways (17, 18).

Both Maynard *et al.* (5) and Heederik *et al.* (7) stated that monitoring respiratory exposure alone might not be sufficient when investigating occupational exposure to soluble platinum and suggested that the dermal route of exposure might also contribute to soluble platinum sensitisation, especially when workers are sensitised at very low airborne concentrations. *In vitro* skin permeation studies have shown very low levels of soluble platinum penetration through full thickness human skin and high retention of platinum within the skin (19, 20). However, the dermal exposure of precious metals refinery workers to soluble platinum has not yet been investigated.

Biological monitoring can be useful since it measures the total absorbed dose as a result of exposure via all routes (21). Urinary platinum excretion is a reliable biomarker of short term

exposure to platinum (22, 23) and has been measured in a number of studies in various occupational settings (22–26). It is used to indicate the total body burden of workers exposed to platinum and also to differentiate between the extent of exposure in different areas (high versus low exposure areas) (22, 23).

The relationship between dermal exposure, respiratory exposure and uptake has been investigated for metals such as cobalt, lead and beryllium (21, 27). Klasson *et al*. (27) concluded that dermal exposure could contribute to the total uptake of cobalt in the same magnitude as respiratory exposure. Respiratory exposure to platinum compounds has been associated with increased urinary platinum excretion (23); however, the contribution of dermal exposure to the total platinum body burden is still unknown. The aim of this study is to quantify the dermal and respiratory soluble platinum exposure at two South African precious metals refineries and to determine the relationship between workers' exposure and their platinum body burden, as determined by the excretion of platinum in the urine. This is the first study to report dermal exposure to soluble platinum in precious metals refineries and is also novel in that it aims to report the relationship between the two exposure routes and platinum body burden.

Materials and methods

Participants

The study was conducted at two South African precious metals refineries between October 2015 and November 2016. Forty workers (32 men and eight women) participated in the study and only workers who were employed at the refineries for longer than one year were included. The average age of the workers was 34.6 ± 7.9 years (range, 22 to 56 years) and the average number of years of employment at the refineries was 7.7 ± 6.3 years (range, 1 to 27 years). Ten persons, who lived >100 km from the nearest platinum industry were included as a control group for the biological monitoring portion of the study. All participants were informed of the details of the study prior to the start and provided written informed consent. Ethics approval for the study was obtained from the Health Research Ethics Committee of the North-West University (NWU-00128-14-A1).

Workers who performed various production and non-production activities in different areas within the refineries were included. The work areas included in the study were: concentrate handling, platinum group metals (PGM) separation, crushing and ignition, precious metals, other precious metals, other production activities (melting and packaging), other non-production

activities (laundry, laboratory and maintenance), security, and health clinic. For the purpose of this study, workers were further divided into groups according to whether they were directly or indirectly exposed to platinum, the number of years they were employed at the refinery and their age. Workers directly exposed to platinum were directly involved with the platinum refining process and came in direct contact with platinum compounds. Those indirectly exposed to platinum worked in the laundry, laboratory, security and health clinic areas where they came into contact with platinum via indirect pathways. Work areas were chosen in such a way that a variety of tasks and exposure scenarios were included and not only high exposure tasks. Workers all used personal protective equipment (PPE) such as hard hats, respiratory protective equipment (RPE) (full-face respirators, half-face respirators or half-face paper dust masks), disposable coveralls and gloves (rubber or latex), as was required by the specific refineries. As part of the refineries' health surveillance programme, all the workers were screened with skin prick tests prior to employment. They were also submitted to regular medical screening and were removed from possible exposure areas if they became sensitised to soluble platinum. With the exception of one of the workers included in the study that has previously experienced minor eczema-type symptoms, none of the participating workers were sensitised to soluble platinum at the time of data collection.

Sample collection overview

The dermal exposure, respiratory exposure and urinary platinum excretion of workers were measured concurrently over two consecutive working days. Dermal and respiratory exposure were measured over the full work shift. For biological monitoring, three spot urine samples were collected from each worker. The first was collected prior to the start of the first day of exposure monitoring, the second prior to the second day of exposure monitoring and the third prior to the start of the following day's shift (28). Schierl *et al*. (26) exposed previously non-exposed volunteers to ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$] dust and reported that their urinary platinum excretions reached the maximum approximately 10 hours after the termination of exposure. Therefore, during this study, the spot urine samples collected on the next morning, approximately 16 hours after the termination of exposure, represented the change in urinary platinum excretion as a result of the previous day's exposure. Finally, surface contamination was assessed on workplace surfaces that workers come into contact with during their routine work activities.

Dermal exposure sample collection

Dermal exposure to soluble platinum was assessed using Ghostwipes™ (SKC, Eighty Four, Pennsylvania, USA), a robust wipe which is moistened with deionised water, individually sealed and that has been used successfully for metals such as nickel, lead and cobalt (29, 30). Prior to the start of the shift, the areas of interest on the skin were cleaned with a wetted wipe, which was discarded. Thereafter, workers performed their normal work activities and were instructed not to wash their hands until the dermal exposure samples were collected. Dermal exposure samples were collected three times during the shift, namely before the tea break, before lunch and at the end of the shift. The platinum content of the three samples collected from each anatomical area was then summed in order to obtain a full shift concentration for each anatomical area. The anatomical areas included were the palm of the hand, wrist and neck on the dominant side of the body as well as the forehead. The same researcher, wearing a clean pair of disposable nitrile gloves for each sample, collected all of the dermal exposure samples. Templates made of acetate paper with a rectangular aperture of 24 cm^2 (6 x 4 cm) were used to demarcate the area were the skin was wiped. The skin was wiped with firm pressure, across the contaminated area with one wipe, covering the entire surface in the template from end to end. A standardised wiping pattern was followed whereby the researcher wiped the demarcated area on the skin with the wipe in an s-motion. The wipe was then folded inward and the area was wiped again in an s-motion rectangular to the first wipe. Then, the wipe was folded again and the first motion repeated. Lastly, the wipe was folded for a third time and the second wiping pattern was repeated. The demarcated area was wiped a total of four times. Each wipe was then deposited in a 50 ml digestion vial (Environmental Express, Charleston, South Carolina, USA) for analysis.

Since Ghostwipes™ have not previously been used to assess dermal exposure to soluble platinum, the recovery and wipe efficiencies were evaluated using three concentrations of ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$] solution which corresponded to spiked masses of 0.005 µg, 0.05 µg and 0.5 µg of platinum, respectively. The mean percentage recovery efficiency for spiked samples was 78.44% (95%CI 68.33-88.54%) and the mean wipe efficiency from a glass surface was 71.56% (95%CI 59.66-83.45%) which complies with the acceptable range of 70% to 120% for recovery and wipe efficiency, as stated in the ISO/TR 14294 technical report (31).

Respiratory exposure sample collection

Personal respiratory exposure to soluble platinum was measured over the entire shift according to the Methods for the Determination of Hazardous Substances (MHDS) 46/2 method (32). A Gilian Gilair Plus air sampling pump (Sensidyne, Clearwater, Florida, USA) was calibrated at a flow rate of 2 l/min and connected to an Institute of Occupational Medicine (IOM) personal sampler (SKC, Eighty Four, Pennsylvania, USA), which was fitted with a mixed cellulose ester membrane filter (SKC, Eighty Four, Pennsylvania, USA). This was placed in the breathing zone of the workers. The mean sample time for respiratory exposure samples were 391 minutes (95%CI: 374-408 minutes) depending on the duration of the workers' shifts.

Biological sample collection

For the biological monitoring of platinum, whole urine samples were collected. A representative 20 ml urine was decanted into a high-density polyethylene bottle (Ampath, South Africa). All urine samples were frozen following collection. For more detail on the biological monitoring sampling procedure please refer to Linde *et al.* (28).

Surface wipe sample collection

The concentration of soluble platinum contamination present on production and non-production surfaces was assessed using Ghostwipes™ and 100 cm^2 (10 x 10 cm) templates. The same wiping procedure was used as during dermal exposure sampling. The surfaces included were tables, railings, door handles and PPE. For irregular shaped surfaces, the dimensions of the wiped area were measured and used to calculate the concentration, which was then normalised to 100 cm^2.

Sample analysis

All dermal and respiratory exposure, and surface wipe samples were analysed for soluble platinum according to a method based on MDHS 46/2 (32) using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). The limit of detection (LOD) for platinum was 0.005 µg per sample. Dermal, respiratory and surface field blank samples for each day of sampling were analysed to confirm the absence of contamination during the sampling procedure. Urine samples were analysed by ICP-MS and the LOD for platinum in urine was 0.1 µg/l.

Statistical data analysis

During statistical analysis, the average of the full shift soluble platinum concentrations (µg/cm^2) measured on the four anatomical positions was used as well as the actual concentrations of (µg/m^3) respiratory soluble platinum exposure over the full shift. The time weighted average (TWA) respiratory exposure concentrations were used to compare exposure to the relevant OELs. In order to correct for dilution, the urinary platinum excretion results were expressed as µg/g creatinine. Statistical analyses were conducted using Statistica version 13.2 (Statsoft Inc., Palo Alto, California, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, California, USA). Respiratory exposure, dermal exposure and biological monitoring measurements which were below the LOD for the specific analytical methods were substituted using β-substitution, a substitution method recommended by Ganser and Hewett (33) for the analysis of censored data. The results for dermal exposure, respiratory exposure and urinary platinum excretion were not normally distributed and were, therefore, log-transformed prior to the statistical analyses. Consequently, the geometric means as well as the 95% confidence interval (CI) of the geometric means were used for the description of the original values. The inter-day variation in the exposure and biological monitoring results was analysed using dependent t-tests and repeated measures analysis of variance (ANOVA), respectively. For the purpose of statistical analyses, workers were grouped into various exposure groups, namely work areas, directly or indirectly exposed to platinum, years employed, age and sex. Independent t-tests, ANOVAs and analysis of covariance (ANCOVA) were used to analyse for statistical differences within these groups of workers. ANOVAs and ANCOVAs with Tukey's post-hoc tests identified statistically significant differences among specific groups. Effect size analyses were used to indicate the practical significance of factors such as work area and years of employment on dermal and respiratory exposure as well as urinary excretion of platinum (34). Partial eta-squared (η^2) values were used to describe the effect of each individual variable on the exposures and urinary platinum excretions of workers. For example, a partial eta-squared value of 0.5 indicated that the specific variable explained 50% of the variation in the exposure or urinary platinum excretion. Partial correlations were performed in order to investigate the relationship between dermal and respiratory exposure to soluble platinum and the urinary platinum excretion of workers while correcting for other variables. For all analyses, $p \leq 0.05$ was considered to be statistically significant.

Results

Workers with a variety of job descriptions working in different areas within the refineries were selected for this study in order to obtain a representative depiction of the dermal and respiratory exposure experienced by workers as well as their platinum body burden. Table 1 contains background information on the study population (n=40) as well as the group divisions and sub-divisions used during statistical analysis.

Table 1: Description of the study population and groupings used for statistical analyses

Group	Subdivisions	Number of workers	%
Work areas	Concentrate handling	6	15
	PGM separation	5	12.5
	Crushing and ignition	4	10
	Precious metals	6	15
	Other precious metals	4	10
	Other production activities	3	7.5
	Other non-production activities	5	12.5
	Security	4	10
	Health clinic	3	7.5
Exposure categories	Direct exposure	30	75
	Indirect exposure	10	25
Years employed categories	1-4	15	37.5
	5-10	15	37.5
	10-20	7	17.5
	≥20	3	7.5
Age categories	20-29	9	22.5
	30-39	22	55
	40-49	7	17.5
	≥50	2	5
Sex	Male	32	80
	Female	8	20
Total		40	100

%, percent of total group of participants.

Table 2: Dermal and respiratory exposure to soluble platinum experienced by workers as well as their urinary platinum excretions

Group		n*	Years employed		Dermal (µg/cm^2)		Respiratory (µg/m^3)		n#	Urine (µg/g creatinine)	
			Range	AM	GM	CI 95%	GM	CI 95%		GM	CI 95%
Work area	Concentrate handling	12	1 - 26	8.67	0.041	0.010 - 0.171	28.180	13.440 - 59.070	18	0.576	0.340 - 0.977
	PGM separation	10	1 - 24	8.00	0.020	0.010 - 0.039	0.419	0.200 - 0.876	15	0.265	0.157 - 0.448
	Crushing and ignition	8	4 - 6	5.00	0.071	0.009 - 0.577	1.919	0.490 - 7.523	12	0.471	0.268 - 0.827
	Precious metals	12	3 - 17	8.83	0.035	0.014 - 0.083	0.746	0.259 - 2.150	18	0.528	0.287 - 0.972
	Other precious metals	8	3 - 8	5.50	0.0006	0.0003 - 0.001	0.021	BDL[b] - 0.117	12	BDL[c]	BDL[c] - 0.111
	Other production activities	6	3 - 12	7.33	0.002	0.0008 - 0.005	0.072	0.007 - 0.711	8	BDL[c]	BDL[c] - BDL[c]
	Other non-production activities	10	2 - 13	8.60	0.002	0.0006 - 0.006	0.030	0.005 - 0.172	15	0.103	BDL[c] - 0.171
	Security	8	3 - 9	6.25	0.006	0.002 - 0.014	0.157	0.017 - 1.480	11	0.106	BDL[c] - 0.146
	Health clinic	6	3 - 15	10.67	BDL[a]	BDL[a] - 0.0004	0.004	BDL[b] - 0.022	9	BDL[c]	BDL[c] - 0.179
Exposure category	Direct exposure	60	1 - 27	7.80	0.014	0.008 - 0.025	0.725	0.357 - 1.472	89	0.285	0.220 - 0.369
	Indirect exposure	20	3 - 15	7.50	0.001	0.0005 - 0.0025	0.022	0.006 - 0.074	29	BDL[c]	BDL[c] - 0.107
Years employed	1-4	30	1 - 4	2.93	0.003	0.002 - 0.007	0.248	0.078 - 0.789	44	0.141	0.111 - 0.179
	5-10	30	5 - 9	6.53	0.013	0.005 - 0.029	0.391	0.146 - 1.049	44	0.244	0.165 - 0.362
	10-20	14	12 - 15	12.86	0.004	0.0007 - 0.018	0.073	0.010 - 0.537	21	0.160	BDL[c] - 0.288
	≥20	6	24 - 27	25.67	0.182	0.051 - 0.646	5.921	0.311 - 112.7	9	1.453	1.184 - 1.783
Age	20-29	18	1 - 8	4.56	0.009	0.004 - 0.023	0.274	0.090 - 0.835	26	0.258	0.153 - 0.434
	30-39	44	1 - 14	6.00	0.006	0.003 - 0.012	0.320	0.119 - 0.860	66	0.176	0.134 - 0.230
	40-49	14	3 - 27	14.14	0.009	0.002 - 0.030	0.226	0.038 - 1.354	20	0.265	0.146 - 0.481
	≥50	4	12 - 26	19.00	0.043	0.0003 - 7.518	0.676	BDL[b] - 3.908	6	0.332	BDL[c] - 2.559
Sex	Male	64	1 - 27	8.00	0.012	0.007 - 0.021	0.594	0.295 - 1.199	95	0.269	0.201 - 0.346
	Female	16	4 - 14	6.63	0.001	0.0004 - 0.003	0.020	0.005 - 0.087	23	BDL[c]	BDL[c] - 0.100
Total		80	1 - 27	7.73	0.008	0.005 - 0.013	0.301	0.151 - 0.601	118	0.212	0.169 - 0.265

n*, Number of dermal and respiratory exposure samples; n#, Number of urine spot test samples; AM, Arithmetic mean; GM, Geometric mean; CI , Confidence interval; BDL, Below detection limit; [a], Dermal detection limit = 0.00021 µg/cm^2; [b], Respiratory detection limit = 0.005 µg/m^3 ; [c], Urine detection limit = 0.1 µg/g creatinine.

Table 2 summarises the dermal and respiratory exposures to soluble platinum as well as the urinary platinum excretions observed during the study. No significant inter-day variation was observed for the dermal exposure (p=0.224), respiratory exposure (p=0.944) or urinary platinum excretion (p=0.262) measurements.

The geometric mean soluble platinum dermal exposure for the total group was 0.008 µg/cm^2 (95%CI: 0.005-0.013 µg/cm^2) with the highest geometric mean concentrations measured in the crushing and ignition [0.071 µg/cm^2 (95%CI: 0.009-0.577 µg/cm^2)] and concentrate handling areas [0.041 µg/cm^2 (95%CI: 0.010-0.171 µg/cm^2)]. The dermal exposure of workers who were directly exposed was significantly higher than those workers who were indirectly exposed (p=0.002). The work area of the workers (p<0.001; η^2=0.700) as well as the number of years employed (p=0.003; η^2=0.258) had a significant effect on their dermal exposure. The workers who were employed more than 20 years at the refineries had a geometric mean dermal exposure of 0.182 µg/cm^2 (95%CI: 0.051-0.646 µg/cm^2).

For the total group of participating workers, the geometric mean respiratory exposure was 0.301 µg/m^3 (95%CI: 0.151-0.601 µg/m^3) with the highest exposure in the concentrate handling [28.180 µg/m^3 (95%CI: 13.440-59.070 µg/m^3)] and crushing and ignition areas [1.919 µg/m^3 (95%CI: 0.490-7.523 µg/m^3)]. The respiratory exposure concentrations reported in Table 2 were not the TWA exposure concentrations. However, when the exposures were averaged over eight hours, 25% of respiratory exposure measurements exceeded the OEL of 2 µg/m^3 for soluble platinum. This OEL is used by countries such as South Africa, the United Kingdom and the Occupational Health and Safety Administration (OSHA) in the United States of America (15, 16, 35). The respiratory exposure of workers who were directly exposed was significantly higher than those who were indirectly exposed (p=0.002) and the work area of the workers had a significant effect on their respiratory exposure (p<0.001; η^2=0.725).

The geometric mean urinary platinum excretion was 0.212 µg/g creatinine (95%CI: 0.169-0.265 µg/g creatinine) and the highest excretions were measured in the concentrate handling area [0.576 µg/g creatinine (95%CI: 0.340-0.977 µg/g creatinine)]. No biological exposure index (BEI®) values are set for platinum compounds. Therefore, the measured concentrations could not be compared to legislative values. The urinary platinum excretion of workers who were directly exposed was significantly higher than those workers who were indirectly exposed (p=0.007). The work area (p<0.001; η^2=0.567) as well as the number of years employed (p=0.003; η^2=0.261) had a significant effect on urinary platinum excretion of workers. Subsequently, the workers who were employed more than 20 years at the refineries had a

geometric mean urinary platinum excretion of 1.453 µg/g creatinine (95%CI: 1.184 – 1.783 µg/g creatinine).

Figure 1 illustrates the distribution of the soluble platinum removed from the various anatomical areas. The anatomical area where the highest geometric mean concentrations were measured for the total group of workers was the palm [0.013 µg/cm^2 (95%CI: 0.008-0.021 µg/cm^2)] followed by the wrist [0.008 µg/cm^2 (95%CI: 0.005-0.015 µg/cm^2)].

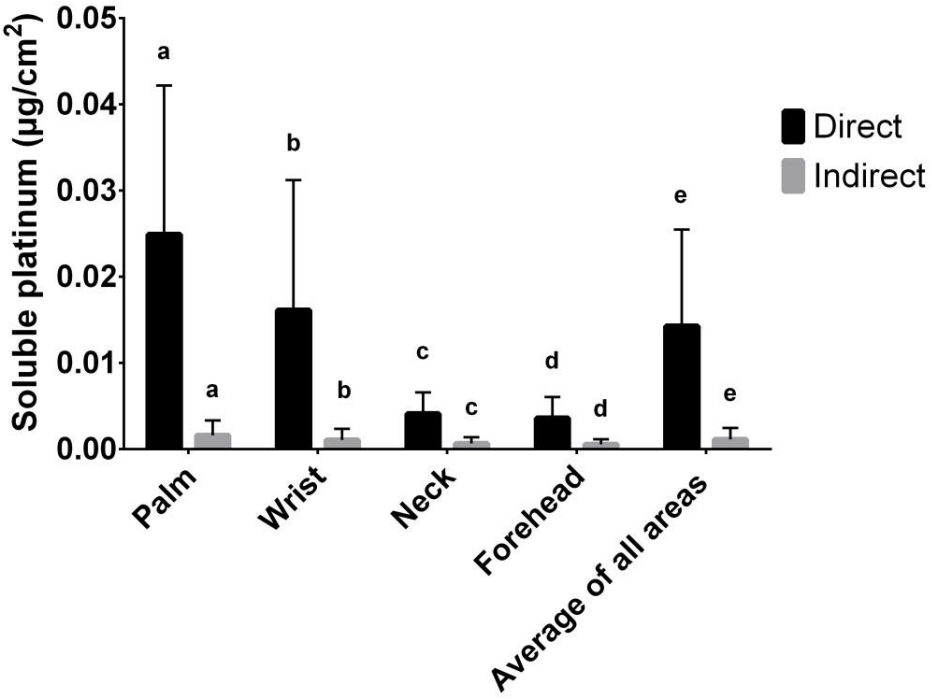

Figure 1: Dermal exposure concentrations removed from various anatomical areas of workers who were directly and indirectly exposed to soluble platinum. Columns indicate geometric means and the vertical lines indicate the 95% CI of the geometric mean. a – e indicates statistically significant differences between workers who are directly and indirectly exposed to platinum compounds ($p < 0.01$ for all anatomical areas).

The relationship between the mean urinary platinum excretion of workers and their mean dermal and mean respiratory exposure to soluble platinum were investigated using partial correlations. These correlations were corrected for the years of employment at the refineries and whether the workers were directly or indirectly exposed to soluble platinum. The correlation coefficients (*r*) were all statistically significant ($p \leq 0.05$) and ranged between 0.580 and 0.754 (Table 3).

Table 3: Correlation coefficients (*r*) of partial correlations between the mean urinary platinum excretion, mean dermal exposure and mean respiratory exposure to soluble platinum for the total group of participating workers

	Dermal exposure (µg/cm^2)	**Respiratory exposure (µg/m^3)**	**Urinary platinum (µg/g creatinine)**
Dermal exposure (µg/cm^2)	-	**0.672**	**0.754**
Respiratory exposure (µg/m^3)	**0.672**	-	**0.580**
Urinary platinum (µg/g creatinine)	**0.754**	**0.580**	-

Statistically significant results are shown in bold ($p \leq 0.05$); Partial correlations were corrected for years of employment and direct or indirect exposure.

All surface wipe samples had detectable levels of soluble platinum. Highly contaminated areas within production areas included sample test areas in PGM separation areas (10.59 and 145.47 µg/cm^2), table surfaces (next to balances) in material concentrate areas (4.80 and 4.55 µg/cm^2), and filter press handles (0.41 and 4.01 µg/cm^2) and glove box lids (0.55 µg/cm^2) in the precious metals areas. Other surfaces in production areas included railings in the concentrate handling area (2.83 and 0.045 µg/cm^2) and the precious metals areas (0.088 µg/cm^2) as well as visibly dirty control room table surfaces (0.12 µg/cm^2). Additionally, contaminated PPE items included hard hats (2.31 µg/cm^2), the inside of protective gloves (0.11 and 0.014 µg/cm^2) and visibly dirty clothing (0.70 and 0.021 µg/cm^2). Finally, other general non-production areas included canteen and health clinic door handles (0.0022 and 0.0060 µg/cm^2), hand railings (0.0034 µg/cm^2) and table surfaces in the canteen (0.0006 µg/cm^2) and health clinic (0.0006 µg/cm^2).

Discussion

This is the first study to report dermal exposure to soluble platinum in an occupational setting and the first to examine the relationship between dermal and respiratory exposure to soluble platinum and platinum body burden, as determined by urinary platinum excretion.

Twenty-five percent of respiratory exposure measurements collected during this study exceeded the OEL of 2 µg/m^3 (15, 16, 36). This is similar to other studies who reported that precious metals refinery workers are often exposed to airborne soluble platinum above the OEL (4, 5, 7). The urinary excretion of workers during this study was comparable to other studies conducted in precious metal refineries such as Farago *et al.* (25) (0.21 to 1.18 µg/g creatinine) and Schierl *et*

al. (26) (0.016 to 6.27 µg/g creatinine). The urinary platinum excretion results are discussed in detail in Linde *et al.* (28).

The mean dermal exposure concentrations from four anatomical areas (palm, wrist, neck and forehead) were used during statistical analyses in order to represent exposure on a variety of anatomical areas. This included areas which were directly exposed (palm and wrist) and those which were indirectly exposed (neck and forehead). This method was used in order to represent dermal exposure on the anatomical areas that were typically exposed to the external environment. It was assumed that dermal exposure took place uniformly across the selected areas and the measurements from the various anatomical areas were, therefore, not weighted to give more prominence to one area compared to another. As is shown in Figure 1, higher concentrations of soluble platinum were measured on the palm and wrist compared to the neck and the forehead. Even though workers used gloves, the highest dermal exposure was observed on the palms of workers which indicated incorrect use of gloves. Surface wipe sampling showed that the insides of gloves were contaminated with soluble platinum. This is not uncommon and other workplace protection studies have shown that contaminants are often present on the inside of protective clothing (37). Surface wipe sampling indicated that various surfaces in production and non-production areas were contaminated with soluble platinum as well. These surfaces could have served as potential sources of respiratory and dermal exposure. It should also be noted that quantifiable concentrations of soluble platinum were removed from the neck and forehead of workers which could be attributed to airborne contaminants settling on the skin. Alternatively, these anatomical areas could have been contaminated by workers touching their neck or forehead with contaminated hands or PPE and thus transferring the contaminants onto those areas. During another dermal exposure study, du Plessis *et al.* (30) also reported the presence of nickel on the neck and forehead of base metals refinery workers while higher concentrations were removed from the palms and index fingers.

Workers' areas of work had a significant effect on their dermal and respiratory exposure as well as their urinary platinum excretion. Statistical analysis with effect sizes showed that 70% of the variation in workers' dermal exposure, 73% of the variation in respiratory exposure and 57% of the variation in urinary platinum excretion could be attributed to their area of work. Also, the dermal and respiratory exposure experienced by workers who were directly exposed to and who directly handled platinum compounds were significantly higher than the exposure experienced by workers who were indirectly exposed during laundry, security and other non-production activities. This result corresponds to other studies who reported increased exposure and

adverse health effects in workers who worked in production areas where soluble platinum compounds were directly handled (4, 8, 11). In a study by Julander *et al.* (38), the dermal exposure of workers to nickel, cobalt and chromium also varied depending on the type of tasks performed and the authors reported higher concentrations of dermal exposure for workers who directly handled metals. In addition to higher exposure, workers who directly handled soluble platinum compounds also had increased urinary platinum excretions compared to those who were indirectly exposed. Similarly, Schierl *et al.* (26) also reported increased urinary platinum excretions for workers who had high respiratory exposure to soluble platinum. The finding that workers who directly handled soluble platinum compounds experienced increased dermal and respiratory exposure as well as increased platinum body burden, could prove beneficial during workplace risk assessments as it can help prioritise the implementation of appropriate exposure control measures.

Additionally, workers who worked in areas of the refineries where no dermal exposure to soluble platinum was expected such as the health clinics, security, laundries and the areas where other PGMs were handled also experienced quantifiable dermal and respiratory exposure to soluble platinum as well as urinary platinum excretion above the LOD in some cases. Although the exposure concentrations were significantly lower than directly exposed workers, these workers still risk developing adverse health effects from soluble platinum exposure. These workers' exposure could have originated from other workers or items from production areas, transporting contaminants into their areas (e.g. dirty clothing of production workers) or from airborne particles entering and settling on surfaces with which workers could come into contact with. Similarly, Klasson *et al.* (27) also reported quantifiable concentrations of cobalt present on the skin of workers who only performed inspections in a hard metal plant. Surface wipe sampling indicated that surfaces (door handles, tables, and railings) in non-production areas (health clinic, canteen and other general areas) were contaminated with detectable concentrations of soluble platinum which could have served as exposure sources.

In addition to the variations in the work areas, the number of years employed at the refineries also had an effect on urinary platinum excretion. After reporting the increased urinary platinum excretion of refinery workers who were not exposed to platinum compounds for two to six years, Schierl *et al.* (26) suggested that a reservoir, similar to what is observed in patients who received anti-cancer treatment with cisplatin (39), might form in workers who were exposed to platinum compounds. Additionally, Franken *et al*. (19) demonstrated during an *in vitro* skin permeation study that the majority of the soluble platinum deposited onto the skin was retained

within the skin, although it was unclear in which layers of the skin the platinum was retained. The authors stated that a reservoir could form inside the skin which could become systemically available with time. Therefore, the increased urinary platinum excretion of workers who were employed for longer periods of time during this study could possibly be due to the absorbed platinum forming a reservoir inside the body, or within the skin following dermal exposure, or a combination of these two reservoirs. In future, investigations using stratum corneum tape stripping might prove useful in studying in which of the skin layers platinum might accumulate following dermal exposure.

Since the dermal exposure, respiratory exposure and biological monitoring were conducted concurrently, the relationship between these routes of exposure and platinum body burden could be assessed. Significant positive correlations were observed between the dermal and respiratory exposures measured for the total study group (directly and indirectly exposed), which indicates that workers who were exposed to increased airborne soluble platinum concentrations were also exposed to increased concentrations via the dermal route of exposure as measured on the four anatomical areas. Dermal exposure could have resulted from airborne particles either settling on the skin of workers or settling on clothing or other surfaces from where it could come into contact with the skin. High correlations between the respiratory exposure and urinary platinum excretion have previously been reported for automotive catalyst production workers (23). Similarly, the partial correlations for the total group of workers during this study revealed a significant positive correlation between increased respiratory exposure to soluble platinum and increased urinary platinum excretion. Likewise, dermal exposure to soluble platinum was also significantly correlated with urinary platinum excretion. Therefore, workers who experienced increased exposure via the respiratory route also experienced increased exposure via the dermal route as well as increased urinary platinum excretion. These significant correlations indicate the significance of not only inhalation but also the skin as a possible route of exposure for soluble platinum.

The effect of PPE on the reduction of exposure can be highly variable and dependent on the correct use of the PPE by the individual (37). Still, the correct use of PPE could contribute to the reduction of exposure. During this study, the use of disposable coveralls by directly exposed workers during high exposure tasks significantly reduced their dermal exposure compared to directly exposed workers who did not use the disposable overalls (p=0.018). Workers from the two refineries used different types of RPE and the effect which RPE might have had on the

absorption of platinum into the body via inhalation is unclear since the respiratory exposure was measured in workers' breathing zone, outside of the RPE.

The effect of ingestion on the urinary platinum excretion is also uncertain. In a recent study investigating the contribution of dermal and respiratory exposure routes to cobalt uptake, the authors stated that unintentional ingestion from hand-to-mouth contact should be considered as a possible route of exposure (27). Gorman Ng *et al.* (40) observed the behaviour of workers in several industries (including a precious metals smelter) and concluded that the time which workers spent in between tasks, their use of PPE, as well as personal factors such as smoking and nail biting influenced the frequency with which there was contact between their hands (or other objects) and their mouths. Studies on occupational exposure to other metals such as lead, cadmium and arsenic have shown that inadvertent ingestion resulting from hand-to-face movements could result in substantial increases in body burden (21). Although inhalation of soluble platinum is of greater importance in terms of health risks compared to ingestion (41), these behavioural factors could lead to inadvertent ingestion and possible increases in platinum body burden. During this study, smoking (n=5) did not significantly affect urinary platinum excretion (p=0.125) but the effect of hand-to-mouth contact and possible food contamination is not clear.

One of the participating workers for this study had previously experienced eczema type symptoms. Other adverse dermal health effects such as urticaria and contact dermatitis have also been reported by precious metals refinery workers (11, 13). Since dermal exposure to soluble platinum has not previously been reported, the exact involvement of dermal exposure to the development of urticaria, eczema or contact dermatitis is unclear and should be investigated further. Precious metals refinery workers are also exposed to acids and other irritant chemicals which could possibly contribute to the development of these adverse effects.

The role of dermal exposure to soluble platinum in respiratory sensitisation in occupational settings is still uncertain (5, 7). Inhalation is the main route of exposure involved in respiratory sensitisation in workplace settings. Yet, there have been indications that respiratory sensitisation is not necessarily an exclusive function of inhalation exposure and it has been suggested that dermal exposure to some chemicals, including soluble platinum, could cause respiratory sensitisation as well. Especially if it involves acute exposure to high concentrations, as is experienced during splashes or spillages (42). Since this paper demonstrated that dermal exposure does take place in precious metals refineries, the involvement of dermal exposure in the development of respiratory sensitisation should be further investigated.

This study was somewhat limited by the high detection limit of the urinary platinum excretion analysis available. The detection limit of 0.1 µg/l was sufficient to investigate the urinary platinum excretion of occupationally exposed persons but was too high to investigate the urinary platinum excretion of those who were exposed to environmental platinum such as the control group. Another limitation was the use of smooth glass plates to evaluate the wipe efficiency of the dermal wipe method which was based on the Occupational Safety and Health Association (OSHA) method ID-125G (29). Since the wipes were used to remove contaminants from the skin of workers, which is uneven and rough, there is a possibility that the levels of soluble platinum were underestimated (43).

Conclusion

Quantifiable concentrations of soluble platinum were measured on the palms, wrist, necks and foreheads of precious metals refinery workers with increased concentrations being measured following direct handling of platinum compounds. Significant positive correlations were observed between both dermal and respiratory exposure routes and platinum body burden, as determined by urinary platinum excretion. Previous exposure studies have only considered the respiratory route of exposure and have confirmed a correlation between respiratory exposure to platinum compounds and urinary platinum excretion. However, soluble platinum has been shown to permeate through intact human skin. The presence of quantifiable concentrations of soluble platinum on the skin of precious metals refinery workers as well as its significant positive correlation with urinary platinum excretion indicates that the skin is a potential route of exposure to soluble platinum and that it should not be ignored when assessing occupational exposure. Additionally the role of dermal exposure in the development of adverse dermal health effects and respiratory sensitisation, as frequently reported in precious metals refineries should be investigated further.

Acknowledgements

We would like to thank the participants and management teams of the respective precious metals refineries for their support.

Disclosures

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions

The manuscript was compiled from contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors, and therefore the NRF does not accept any liability in regards thereto. The authors declare no competing financial interest.

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CHAPTER 6: ARTICLE IV

Linde SJL, Franken A, du Plessis JL. (2017) Effectiveness of disposable coveralls in reducing dermal exposure to platinum. To be submitted to the journal *Annals of Work Exposures and Health* to be considered for publication.

6.1 Background

Personal protective equipment (PPE) is often used to protect workers against exposure to hazardous chemicals in areas where exposure is not adequately controlled by other measures. However, questions are frequently asked regarding the effectiveness of PPE in reducing exposure. The effect that the use of disposable coveralls and PPE usage procedures in precious metals refineries had on the dermal exposure of workers' to soluble platinum was assessed using the dermal exposure, respiratory exposure and urinary platinum excretion data reported in Atricle III. This article is written in the form of a "short communication" as is described in Section 6.2. below.

6.2 Instructions to authors (excerpt)

Annals of Work Exposures and Health publishes original research and development material that helps reduce risk of ill-health resulting from work, and welcomes submissions in these areas.

Short communications are descriptive studies, with limited data that present new information of importance to the readership but with insufficient data for a full original research report. Examples include: a description of an occupational disease case with a thorough investigation of the exposures likely to have given rise to the disease; a demonstration of a new measurement principle or device with potential for solving an important exposure measurement problem; evidence demonstrating the effectiveness of a novel exposure control strategy. In each case, the data available are insufficient to support a full original research paper or prove the validity of the observation, but provide potentially important information to occupational hygienists. Short communications will generally be less than 1500 words and have up to two tables or figures. Such reports will be peer reviewed through our normal process.

Language: Manuscripts must be in English and authors should try to write in a way which is simple and clear. British or American styles and spelling may be used, but should be used consistently, and words or phrases which might be unclear in other parts of the world should be avoided or clearly explained. It is the authors' responsibility to provide a text in good English.

Manuscript format: Papers should generally conform to the pattern: Introduction, Methods, Results, Discussion, and Conclusions, unless these are clearly inappropriate. A paper must be prefaced by an abstract of the argument and findings, which may also be arranged under the same headings. As with many other journals, we are unable to publish footnotes to the text. Please therefore incorporate this sort of material into the body of the paper, in brackets if appropriate.

Tables: Tables should be numbered consecutively and given a suitable caption. As with Figures, it is helpful to incorporate them into the text of the first submission, but in the revised version each table should be presented on a separate page. Footnotes to tables should be provided below the table and should be referred to by superscript lowercase letters

Figures: These include photographs, diagrams and charts. The first submission should include good quality low resolution copies of Figures, and may be incorporated into the text or at the end of the manuscript.

References: References should only be included which are essential to the development of an argument or hypothesis, or which describe methods for which the original account is too long to be reproduced. References in the text should be in the form Jones (1995), or Jones and Brown (1995), or Jones et al. (1995) if there are more than two authors, and they should be incorporated naturally into the text. For example:
Jones and Brown (1995) and Hospath et al (2006) observed total breakdown of control..., or
Total breakdown of control has sometimes been observed (Jones and Brown, 1995; Hospath et al., 2006).

At the end of the paper, references should be listed in alphabetical order by name of first author, using the Harvard Style of abbreviation and punctuation. ISBNs should be given for books and other publications where appropriate. Material unobtainable by readers should not be cited. Personal Communications, if essential, should be cited in the text (e.g., Professor O.H. Poobah,

Institute for Dusty Sciences). Internet material can be referred to if it is likely to be permanently available; the date on which it was last accessed should be given. References will not be checked editorially, and their accuracy is the responsibility of authors.

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6.3 Effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum

Abstract

Background. Occupational exposure to soluble platinum is associated with adverse respiratory health effects and skin conditions. Dermal exposure to soluble platinum has recently been reported in precious metals refineries.

Objectives. To assess the effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum.

Methods. The dermal and respiratory exposure to soluble platinum and urinary platinum excretion of 30 precious metals refinery workers, who were directly exposed to platinum compounds, were assessed over two consecutive days. Dermal exposure was assessed using Ghostwipes™, personal respiratory exposure was measured using the Methods for the Determination of Hazardous Substances 46/2 method and urinary platinum excretion was assessed with spot urine sampling. All samples were analysed using Inductively Coupled Plasma-Mass Spectrometry. Workers were divided into two groups. Group A wore disposable coveralls over standard poly-cotton overalls and followed strict usage procedures for personal protective equipment (PPE). Group B workers only wore standard poly-cotton overalls and did not follow strict usage procedures.

Results. Workers from group A experienced significantly lower ($p = 0.018$) dermal exposure [geometric mean = 0.005 µg/cm^2; 95% confidence interval (CI) = 0.002-0.010 µg/cm^2] compared to workers from group B (geometric mean = 0.033 µg/cm^2; 95% CI = 0.015-0.070 µg/cm^2). No significant differences were observed for respiratory exposure ($p = 0.789$) and urinary platinum excretion ($p = 0.273$) between the two groups, although a lower tendency was observed for the urinary platinum excretion of group A workers.

Conclusions. Disposable coveralls, along with the strict adherence to PPE usage procedures proved effective in reducing the dermal exposure of workers to soluble platinum.

Key words:
Urinary platinum; personal protective equipment; skin exposure; Ghostwipes™; MDHS 46/2; platinum salt sensitisation.

Introduction

Occupational respiratory exposure to soluble platinum is associated with the development of soluble platinum sensitisation and numerous studies have reported concentrations of airborne soluble platinum in workplaces (Hunter *et al.*, 1945; Calverley *et al.*, 1995; Maynard *et al.,* 1997; Cristaudo *et al.*, 2007; Heederik *et al.,* 2016). Respiratory exposure to soluble platinum has been correlated with urinary platinum excretion (Cristaudo *et al.*, 2007) and recently, dermal exposure to soluble platinum has also been correlated with the urinary platinum excretion of precious metals refinery workers [Linde *et al.,* 2017b (submitted)]. It has been demonstrated that small amounts of soluble platinum can permeate through human skin (Franken *et al.,* 2014) and skin conditions such as contact urticaria, contact dermatitis and eczema have been observed in workplaces where soluble platinum is handled (Hunter *et al.*, 1945; Santucci *et al.*, 2000; Cristaudo *et al.*, 2005). The effectiveness of disposable coveralls to reduce exposure to pesticides has been reported (Garrigou *et al*., 2011); however, its effectiveness in reducing soluble platinum exposure has not yet been established.

The control of occupational dermal exposure using engineering controls is always preferred to personal protective equipment (PPE) (Cherrie *et al.,* 2010). The effectiveness of PPE is dependent on its correct selection, use and maintenance, and contamination is often reported to be present on the inside of gloves and other PPE (Evans *et al.,* 2001; Cherrie *et al.,* 2010). However, the use of PPE may, in some cases, be required because other control measures may be inappropriate or impossible to implement due to financial constraints (MacFarlane *et al.*, 2013).

The aim of this study was to investigate the effectiveness of disposable coveralls in reducing precious metals refinery workers' dermal exposure to soluble platinum.

Methods

Participants

Thirty workers from two South African precious metals refineries were included in this study and all the workers were directly exposed to platinum compounds during the refining process. All workers used PPE as was required by the specific refineries. As is indicated in Table 1, one group of workers (Group A) wore Microgard® 2000 Standard disposable coveralls (Microgard Ltd, Kingston Upon Hull, United Kingdom) over their standard poly-cotton overalls while carrying out high exposure tasks, while the other group of workers (Group B) only wore standard poly-

cotton overalls. The poly-cotton overalls consisted of a long-sleeved jacket with a pair of trousers while the disposable coveralls were one piece suits with long sleeves, long legs and a hood. Table 1 summarises the background information on the two groups and the PPE they used.

Table 1: Background information and PPE used by the two groups of workers who participated in this study

Group	n	Years employed		PPE		
		AM	Range	Clothing	Gloves	RPE
Group A	13	3.83	1 - 7	Microgard® 2000 Standard disposable coveralls + standard poly-cotton overalls	Long sleeve rubber gloves	Half-face respirators
Group B	17	10.82	3 – 27	Standard poly-cotton overalls	Nitrile gloves	FFP_2 paper dust masks + Half-face respirators

n, Number of workers; AM, Arithmetic mean; PPE, Personal protective equipment' RPE, Respiratory protective equipment.

Ethics approval for the study was obtained from the Health Research Ethics Committee of the North-West University (NWU-00128-14-A1).

Sampling methodology

Dermal exposure, personal respiratory exposure and biological monitoring were conducted concurrently over two consecutive working days. The sample collection strategy is reported in Linde *et al.* (2017a) (submitted) and Linde *et al.* (2017b) (submitted), but in short:

Dermal exposure to soluble platinum was assessed using Ghostwipes™ (SKC, Eighty Four, Pennsylvania, USA) on demarcated areas on the palm of the hand, wrist, neck and forehead of workers. Samples were collected prior to the tea break, lunch break and at the end of the shift. The platinum content of these samples was summed to obtain a full shift concentration for each anatomical area. Full shift personal respiratory exposure to soluble platinum was conducted using the Methods for the Determination of Hazardous Substances (MHDS) 46/2 method (HSE, 1996). Biological monitoring was performed by measuring the urinary platinum excretion of workers. Three spot urine samples were collected for each worker (in the morning prior to the first and second days of exposure monitoring, and again prior to the following day's shift). All samples were analysed using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).

Statistical analysis

The average of the full shift soluble platinum concentrations (µg/cm^2) measured on all four anatomical areas was used to represent the dermal exposure per shift. Additionally, the airborne concentrations of soluble platinum (µg/m^3) measured on the two sampling days as well as the platinum content of the three individual spot urine samples were used during statistical analysis. Statistical analyses were conducted using Statistica version 13.2 (Statsoft Inc., Palo Alto, California, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, California, USA). All measurements that were below the limit of detection (LOD) were substituted using β-substitution (Ganser and Hewett, 2010). Dermal exposure, respiratory exposure and urinary platinum excretion data were not normally distributed and were, therefore, log-transformed prior to the statistical analyses. Statistical analysis included independent t-tests, to analyse for statistical differences between the groups of workers, as well as analysis of covariance (ANCOVA) with partial eta-squared (η^2) values to describe the influence of the years' experience on the exposure and biological monitoring results ($p \leq 0.05$ was considered to be statistically significant).

Results and discussion

The influence of the disposable coveralls on the exposure of workers to soluble platinum was investigated through comparison of the exposure concentrations and urinary platinum excretion of two groups of workers (group A and B) who were directly exposed to soluble platinum. Group A wore the disposable coveralls during high exposure tasks and Group B only wore the standard poly-cotton overalls. The dermal and respiratory exposures to soluble platinum and urinary platinum excretion of the two groups are illustrated in Figure 1.

Figure 1 shows that the two groups of workers were exposed to comparable concentrations of airborne soluble platinum ($p = 0.789$) (Figure 1a) but that group A experienced significantly lower dermal exposure ($p = 0.018$) (Figure 1b). According to the manufacturer, the Microgard® 2000 Standard disposable coveralls provide a barrier against liquids and particles larger than 0.01 µm (Microgard Ltd, 2017). The disposable coveralls prevented the airborne soluble platinum from settling on the skin and clothing of workers during high exposure tasks and reduced the contact of the skin with contaminated surfaces. The sleeves of the disposable coveralls were tucked into the long-sleeved rubber gloves (Table 1). In comparison, Group B used standard nitrile gloves and a gap was visible between the sleeves of the workers' jackets and the gloves where soluble platinum could have deposited on the skin.

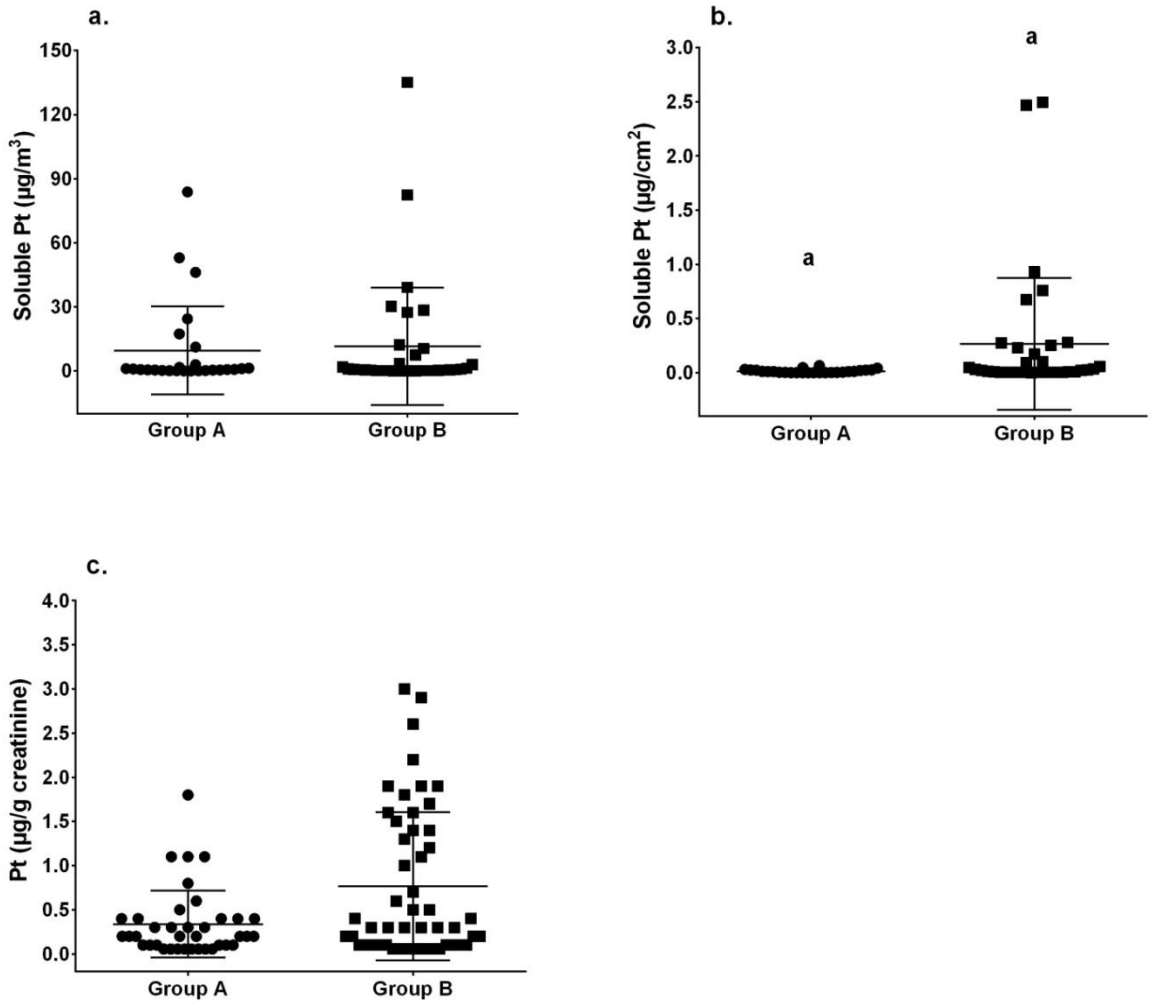

Figure 1: Comparison between the individual (a) respiratory exposure, (b) dermal exposure and (c) urinary platinum excretion measurements of directly exposed workers who used disposable coveralls (Group A) and those who only used standard overalls (Group B). The horizontal lines in the centre of the graphs indicate the geometric mean while the upper and lower limits indicate the 95% confidence intervals of the geometric means. * indicates a statistical difference (p = 0.018).

Figure 2 illustrates the difference between the soluble platinum dermal exposure measured on the four anatomical areas of the two groups of workers. Significant differences were observed between the soluble platinum concentrations on the palms (p = 0.017), wrists (p = 0.017) and foreheads (p = 0.027) of workers as well as for the average of all four areas (p = 0.018).

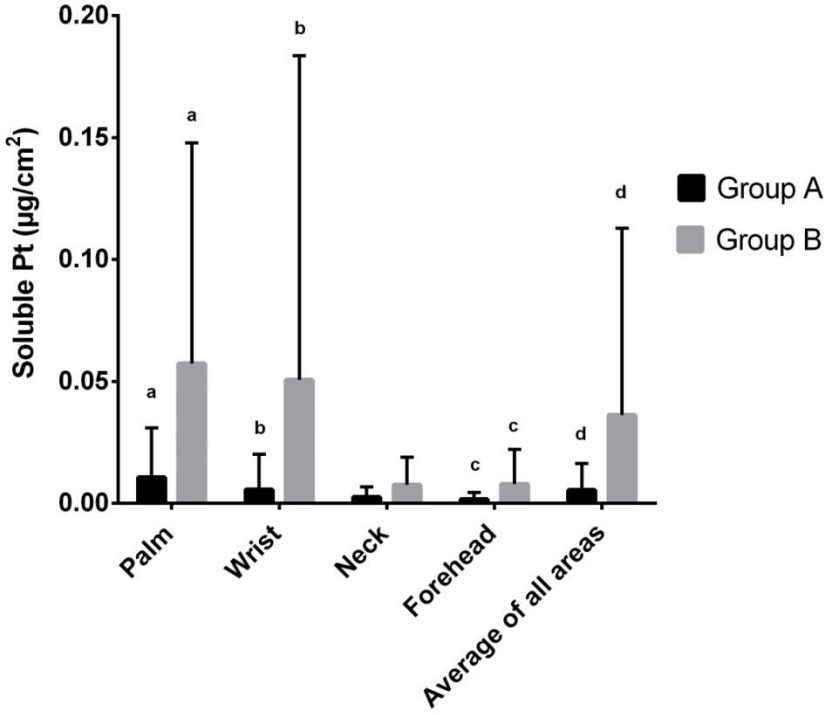

Figure 2: Comparison between the soluble platinum concentrations removed from the skin of directly exposed workers who used disposable coveralls (Group A) and those who only used standard poly-cotton overalls (Group B). Columns indicate the geometric mean while the upper limits indicate the 95% confidence interval of the geometric means. Statistical differences were identified for the palm, wrist, forehead and the average of all areas ($p \leq 0.05$) and are indicated above each column.

Although the urinary platinum excretion of workers from Group A was not significantly lower ($p = 0.273$), there was a lower tendency for Group A [geometric mean (GM) = 0.208 µg/g creatinine; 95% confidence interval (CI) = 0.150-0.288 µg/g creatinine] compared to the urinary platinum excretion of workers from group B (GM = 0.361 µg/g creatinine; 95% CI = 0.247-0.526 µg/g creatinine) (Figure 1c). It was observed that the Group A workers consciously performed a well drilled ritual of donning the necessary PPE (Table 1) before performing high exposure tasks such as scooping wet platinum salt from glove boxes or pouring concentrate into the reactors, while Group B workers did not execute the same degree of preparation before performing high exposure tasks. Additionally, some of the workers from Group B were observed to remove their jackets during high exposure tasks which left the wrists and forearms exposed. It is likely that the ritualistic act of donning the disposable coveralls and other PPE before carrying out high exposure tasks increased the workers' awareness of health and safety procedures which led to more effective use of the PPE and subsequent lower dermal exposure and lower tendency in

urinary platinum excretion. Furthermore, the ANCOVA revealed that years' experience significantly influenced the urinary platinum excretion of workers ($p = 0.042$; $\eta^2=0.144$). Workers from Group A were employed for shorter periods compared to Group B (Table 1). The years workers were employed could have influenced the way work procedures were followed by the different groups of workers. Less experienced employees could be more careful in adhering to protocols such as the donning of PPE while more experienced employees were possibly more careless. Figure 2 shows that significantly higher concentrations of soluble platinum were removed from the palms of Group B workers. This suggests that it was not only the use of disposable coveralls but also the strict execution of PPE procedures and effective use of gloves that reduced the dermal exposure of Group A workers.

Following a shift, all contaminated clothing is transported to the laundry areas of the precious metals refineries where laundry workers can potentially be exposed to soluble platinum. The use of disposable overalls can reduce the contamination of poly-cotton overalls and subsequently reduce the exposure of laundry workers. Discarded coveralls can then be processed along with other platinum containing waste following the shift.

Conclusions

Dermal exposure to soluble platinum is a relevant hazard in precious metals refineries and although the use of PPE to reduce exposure is considered a last resort, it is widely used in workplaces where other control measures do not effectively reduce exposure. During this study, the use of disposable coveralls, along with strict usage procedures, proved effective in reducing precious metals refinery workers' dermal exposure to soluble platinum. It is recommended that disposable coveralls be used in high exposure areas, along with engineering and administrative control measures, to reduce workers' exposure to soluble platinum. Workers should be thoroughly trained in exposure reduction procedures such as donning and doffing of disposable coveralls and other PPE and these procedures should be strictly adhered to. Disposable coveralls have the additional advantage of reducing the contamination of standard poly-cotton overalls and the subsequent transport of contaminants to the laundry areas.

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CHAPTER 7: CONCLUSIONS, RECOMMENDATIONS, LIMITATIONS AND FUTURE STUDIES

In this chapter, the conclusions of this thesis, its limitations as well as the recommendations for control measures and future studies, are provided. Specific reference is made to the aims, objectives and hypotheses, as stated in Chapter 1. Recommendations are given on how to improve the reporting of occupational respiratory exposure monitoring data as well as on measures that can be used to control respiratory and dermal exposure to platinum compounds at the specific precious metals refineries used in this study as well as precious metals refineries in general. Finally, the limitations of this study as well as potential future studies are discussed.

7.1 Conclusions

7.1.1 Review of occupational respiratory exposure to platinum group metals

The general impression within the platinum industry is that respiratory exposure to platinum group metals (PGMs) is well characterised and that the body of literature available provides an effective basis from which decisions can be made to protect worker health. The first objective of this thesis was to critically review the available literature on respiratory exposure to PGMs in occupational settings (Chapter 1, Section 1.2.2). The review of the published literature regarding occupational respiratory exposure to PGMs can be found in a review article (Chapter 3), which was published in the journal *Chemical Research in Toxicology* (Linde *et al.*, 2017). This review article highlighted some limitations in the published body of literature which has investigated occupational exposure to PGMs. The first study to measure occupational respiratory exposure to PGMs was published in 1945 (Hunter *et al.*, 1945). Since then a relatively small number of research papers reporting occupational respiratory exposure to PGMs have been published with very few papers reporting respiratory exposure to PGMs other than platinum. Of the published research papers only a few truly characterise exposure while others only report summarised data. The concentrations of airborne soluble platinum from personal and area monitoring reported by these papers were represented graphically in Chapter 3 (Figure 1) to indicate that the highest concentrations of airborne soluble platinum are present in precious metals refineries. No standardised approach for reporting respiratory exposure monitoring data could be identified which made the comparison of studies challenging. Some research papers only reported the percentage of exposure measurements that exceeded the generally accepted occupational exposure limit (OEL) of 2 µg/m^3 (Brooks *et al*., 1990; Linnett *et*

al., 1999; Merget *et al.,* 2000) because their main focus was medical surveillance and not exposure characterisation. Additionally, there were differences in reporting whether soluble or metallic PGMs were measured. Some papers only reported exposure to total PGMs and others reported exposure to soluble PGMs. This influences the interpretation of results since soluble platinum compounds are more toxic compared to platinum metal, which is considered to be inert (Wiseman and Zereini, 2009). Furthermore, some studies used area measurements to categorise the airborne concentrations of soluble platinum to which workers were exposed to instead of personal exposure measurements (Hunter *et al*., 1945; Brooks *et al.,* 1990; Bolm-Audorf *et al*., 1992). The factors that were identified to have influenced respiratory exposure to PGMs included the type of industry where exposure took place, whether soluble or metallic PGMs were measured and the tasks that were performed in the specific work areas. The highest concentrations of airborne soluble platinum were measured in precious metals refineries where exposures of workers to soluble platinum frequently exceeded the OEL (Calverley *et al.,* 1995; Heederik *et al*., 2016), especiallyduring the direct handling of PGM salts (Hunter *et al.,* 1945).

As discussed in Section 10 of Chapter 3, the occupational health and safety legislation applicable to occupational exposure to soluble platinum is out-dated and has remained unchanged since 1970 (Heederik *et al*., 2016; ACGIH, 2001). A reduction in the OEL to as low as 5 ng/m^3 has been proposed by organisations such as the Dutch Expert Committee on Occupational Standards (DECOS, 2008) but has been met with opposition by Bullock (2010), as discussed in Chapter 3. Although there has not yet been consensus regarding the exact reduction in the OEL that should be implemented, the platinum industry through organisations such as the International Platinum Group Metals Association (IPA) have recognised that workers are still being sensitised to soluble platinum and as a result, some of its member companies are starting to implement a “best practice” exposure limit of 1 µg/m^3 (Professor C.J. Badenhorst, Anglo American). Additionally, only a few countries or organisations have classified soluble platinum as respiratory and/or dermal sensitisers, although there is evidence that occupational exposure to soluble platinum compounds does cause allergic reactions (Bolm-Audorff *et al*., 1992; Cristaudo *et al*., 2007; Heederik *et al*., 2016) (See Table 3 of Chapter 3 for list of countries).

7.1.2 Biological monitoring of platinum

The urinary platinum excretion of workers has been reported for precious metals refineries and automotive catalyst production plants in Europe, United Stated of America (USA) and the United Kingdom (UK) (Johnson *et al*, 1976; Farago *et al.*, 1998, Schierl *et al.,* 1998; Cristaudo *et al.,* 2007), but not for South Africa, the largest producer of platinum in the world (Johnson Matthey, 2017). The second objective of this thesis was to assess the platinum body burden of workers through the analysis of the platinum concentration present in their urine. Chapter 4 of this thesis presented the urinary platinum excretion of forty South African precious metals refinery workers over a period of 48 hours and was submitted for publication in *Occupational and Environmental Medicine*. Some of the workers included in this study were directly exposed to platinum compounds (process operators, maintenance personnel, etc.) and others were indirectly exposed (laundry workers, security guards, health clinic workers, etc.). The results indicated no significant differences in urinary platinum excretion between sampling days which corresponded to Schierl *et al.* (1995) who reported low variability in the urinary platinum excretion of persons who underwent chemotherapy with cis-platin. The low variability described in Chapter 4 confirms that spot urine samples can be used to investigate the platinum body burden of workers who are exposure to platinum compounds.

In Chapter 1 it was hypothesised that (i) the urinary platinum excretion of workers from South African precious metals refineries is comparable to that of precious metals refinery workers from other countries. Chapter 4 reported that the urinary platinum excretion of the precious metals refinery workers ranged from < 0.10 to 3.00 µg/g creatinine (geometric mean = 0.21 µg/g creatinine). This is comparable to other biological monitoring studies conducted in precious metals refineries in Europe (0.016 to 6.270 µg/g creatinine) (Schierl *et al.,* 1998), the UK (0.21 to 1.18 µg/g creatinine) (Farago *et al.,* 1998) and the USA (< 0.1 to 2.58 µg/l) (Johnson *et al*, 1976).The hypothesis is, therefore, accepted.

Additionally, it was hypothesised that (ii) workers who are directly exposed to platinum compounds have increased urinary platinum excretion compared to workers who are indirectly exposed. The results from the biological monitoring study showed that the urinary platinum excretion of workers who were directly exposed to platinum compounds were significantly higher ($p = 0.007$) compared to those who were indirectly exposed. This hypothesis is, therefore, accepted. The information above indicates that urinary platinum excretion can be used to differentiate between groups of workers who are directly and indirectly exposed to

platinum compounds. This conclusion echoes the statement of other studies such as Petrucci *et al*. (2005) that urinary platinum excretion is a reliable biomarker of exposure to platinum.

7.1.3 Respiratory and dermal exposure to soluble platinum

As is discussed in Section 4 of Chapter 3 of this thesis, occupational exposure to soluble platinum may lead to the development of adverse effects of the respiratory tract and the skin. Yet, the dermal exposure to soluble platinum has not been reported previously and exposure studies have focused exclusively on respiratory exposure. Objectives iii, iv and v of this thesis were to assess the respiratory and dermal exposure of precious metals refinery workers to soluble platinum, and to examine the relationship between these routes of exposure and urinary platinum excretion in order to establish the contribution of each route of exposure to the platinum body burden. Chapter 5 of this thesis presented the findings of the first study to concurrently measure respiratory and dermal exposure to soluble platinum as well as urinary platinum excretion in an occupational setting. Chapter 5 has been submitted for publication in the journal *Contact Dermatitis*. The respiratory and dermal exposure and urinary platinum excretion of forty workers from two South African precious metals refineries were measured over two consecutive working days. The average time weighted average (TWA) respiratory exposure of the total group of workers over the two consecutive working days ranged from < 0.005 to 73.27 µg/m^3 (geometric mean = 0.30 µg/m^3). Their average dermal exposure, as measured on the palm, wrist, neck and forehead using the commercially available Ghostwipes™ ranged from < 0.00021 to 1.70 µg/cm^2 (geometric mean = 0.008 µg/cm^2). In Chapter 1 of this thesis, it was hypothesised (iii) that South African precious metals refinery workers are exposed to soluble platinum via the respiratory exposure route and that detectable concentrations of soluble platinum are present on the skin of workers. The findings from the respiratory and dermal exposure assessment indicate that this hypothesis can be accepted.

The work areas of workers had the greatest effect on the variation seen in their respiratory exposure (73%), dermal exposure (70%), and urinary platinum excretion (57%). The highest geometric mean respiratory exposure was seen for the group of workers in the concentrate handling area (28.18 µg/m^3) while the highest geometric mean dermal exposure was seen for the group of workers in the crushing and ignition areas (0.071 µg/cm^2) and the highest geometric mean urinary platinum excretion was seen for the group of workers in the concentrate handling area (0.576 µg/g creatinine). In general, a clear distinction could be made between the exposure and urinary platinum excretion of workers who were directly exposed to platinum

compounds and those that were indirectly exposed. Although directly exposed workers have a higher risk for exposure, other indirectly exposed workers, such as security guards and other non-production workers were also exposed via both exposure pathways and had detectable levels of urinary platinum excretion.

7.1.4 Contribution of exposure routes to platinum body burden

Respiratory exposure to platinum compounds has previously been positively correlated with workers' urinary platinum excretion (Cristaudo *et al.,* 2007). In Chapter 1 it was hypothesised that (iv) that respiratory and dermal exposure of South African precious metals refinery workers to soluble platinum correlates positively with their platinum body burden (as reflected by the urinary platinum excretion). Chapter 5 of this thesis shows the statistically significant positive correlations between respiratory exposure and urinary platinum excretion ($r = 0.580$) and between dermal exposure and urinary platinum excretion ($r = 0.754$). These findings indicate that this hypothesis can be accepted and that respiratory as well as dermal exposure should be considered when investigating occupational exposure to platinum compounds.

The respiratory exposure to soluble platinum experienced by the precious metals refinery workers during this study was significantly positively correlated with their dermal exposure ($r = 0.754$) (Chapter 5). This suggests a link between respiratory and dermal exposure and shows that working in areas with increased concentrations of airborne soluble platinum led to increased dermal exposure in these refineries. Dermal exposure occurred through the deposition of soluble platinum from airborne particle emission sources such as mechanical sieves, sample splitters, concentrators, sweeping and the pouring of material and through contact with contaminated surfaces such as filter press handles and contaminated personal protective equipment (PPE). The correlation between respiratory and dermal exposure suggest that dermal exposure was chiefly caused by airborne contaminants depositing onto the skin, clothing or onto surfaces from where it could be transferred onto the skin by direct contact. None of the workers in any of the workplaces included in this study were only exposed via one exposure route. It is evident that the respiratory and dermal exposure routes cannot be separated in these workplaces and that they influence one another. These exposure scenarios, therefore, stress the importance of a total exposure assessment approach and the consideration of all exposure routes when assessing and controlling exposure in the workplace.

There is evidence in literature that the dermal exposure route is relevant for soluble platinum compounds. Roshchin *et al.* (1984) reported that ammonium hexachlorplatinate was absorbed

in the systemic circulation of guinea pigs following topical application and Franken *et al.* (2014) reported that low amounts of platinum permeated through intact human skin during *in vitro* experiments. Additionally, there are indications that development of occupational respiratory sensitisation does not result exclusively from inhalation exposure (Kimber and Dearman, 2002). It has been postulated that dermal exposure could contribute to respiratory soluble platinum sensitisation (Maynard *et al.*, 1997; Heederk *et al.*, 2016) and the topical application of platinum salts onto the skin of mice have resulted in immune responses similar to those elicited by other allergens that cause respiratory immune responses following epicutaneous application (Dearman *et al.,* 1998). However, the exact role of dermal exposure in the development of soluble platinum sensitisation in precious metals refineries is not yet understood. The correlation between dermal exposure and platinum body burden as observed in this study places focus on the presence of dermal exposure in precious metals refineries and the possible role it could play in soluble platinum sensitisation. The IPA's scientific task force recently placed dermal exposure and its role in the development of soluble platinum sensitisation on its list of priority research topics (Professor C.J. Badenhorst, Anglo American). The confirmation of the occurrence of dermal exposure in precious metals refineries and its possible contribution to platinum body burden, therefore, contributes to a very actual issue that could impact a substantial portion of the 172 310 workers who are employed in the South African PGM mining sector (Chamber of Mines of South-Africa, 2017). It could also have an impact on the risk management and exposure control measures of precious metals refineries and other industries where workers are exposed to soluble platinum.

7.1.5 The influence of personal protective equipment on exposure

Even though workers used the required gloves and other PPE as prescribed by the management teams of the respective refineries, the highest geometric mean of soluble platinum concentration on the skin of the directly exposed workers was observed on the palm of the hand (0.013 µg/cm^2). The second highest exposed area was the wrist (0.008 µg/cm^2), followed by the neck (0.003 µg/cm^2) and the forehead (0.002 µg/cm^2). It has to be noted that concentrations of soluble platinum above the detection limit were removed from the necks and foreheads of workers. Therefore, the risk of dermal exposure does not exclusively apply to anatomical areas that come into direct contact with contaminants but also to areas of the body that can be contaminated through the transfer of contaminants from the hands or through the settling of airborne contaminants onto the skin.

Objective vi of this thesis was to assess the effectiveness of disposable coveralls in reducing dermal exposure to soluble platinum. Chapter 6 of this thesis found that workers who were directly exposed to platinum compounds and wore disposable coveralls over standard poly-cotton overalls experienced significantly lower dermal exposure compared to directly exposed workers who only wore the standard poly-cotton overalls. Workers who wore the disposable coveralls also strictly followed usage procedures which included the proper donning of PPE before high exposure tasks and proper doffing afterwards, which lead to a lower tendency in their urinary platinum excretion. Therefore, the use of disposable coveralls and the strict adherence to PPE usage procedures contributed to reducing dermal exposure to soluble platinum and could also have led to a reduction in urinary platinum excretion. Furthermore, Chapter 6 showed that urinary platinum excretion can be used as an additional tool to evaluate the effectiveness of the control measures, work procedures and PPE to reduce intake of platinum compounds.

7.1.6 Summary

The comprehensive characterisation of exposure via several exposure pathways is the first step towards developing biologically relevant exposure indices. Once exposure has been fully characterised, other questions or hypotheses concerning the importance of these exposure routes and the development of specific adverse health effects can be examined (Day *et al.*, 2009). The present study confirmed the presence of soluble platinum on the skin of precious metals refinery workers and established significant positive correlations between dermal exposure and urinary platinum excretion as well as respiratory exposure and urinary platinum excretion (Chapter 5). Previously, increased urinary platinum excretion has been correlated with increased respiratory exposure in automotive catalyst production plants (Cristaudo *et al.*, 2007). Also, respiratory exposure has been shown as a risk factor for the development of soluble platinum sensitisation (Heederik *et al.*, 2016). Since the relevance of respiratory exposure has already been established, the findings of the present study places the focus on dermal exposure and its relevance in precious metals refineries, which has not received much attention up to now.

In conclusion, the general aim of this thesis, namely to evaluate respiratory and dermal exposure to soluble platinum of South African precious metals refinery workers and to examine the contribution of each exposure route to the platinum body burden of workers has, therefore, been achieved.

7.2 Recommendations

The execution of the objectives of this study led to the identification of recommendations that could reduce the occupational exposure of precious metals refinery workers to soluble platinum. As is discussed in Chapter 3, the intensity or degree of exposure to soluble platinum is the greatest risk factor for developing soluble platinum sensitisation (Heederik *et al.*, 2016). Merget *et al.* (2017) has demonstrated through follow-up medical examinations that simply removing workers from high exposure areas once they are sensitised to soluble platinum does not necessarily protect them from experiencing asthma years following their last exposure event. Therefore, the best way to protect workers against being sensitised is to reduce the concentration of soluble platinum to which they are exposed to while performing their duties. The following section contains recommendations made to the precious metals refineries where the monitoring was conducted as well as recommendations that are applicable to precious metals refineries in general. Section 10 and 11 of the Hazardous Chemical Substances Regulations states that the employer shall control the exposure of an employee by limiting the amount of a hazardous chemical substance that the employee is exposed to, by limiting the duration of exposure and by making use of engineering (e.g. local extraction ventilation) and administrative (e.g. work procedures) control measures. Lastly, PPE should be provided if exposure cannot be adequately controlled (DOL, 2017). The recommendations below are listed in an order that reflects the above mentioned hierarchy as well as the practicability of the implementation of the measures in the precious metals refineries.

- *Recommendation 1:* Section 14 of Chapter 3 of this thesis contains recommendations for the standardisation of the reporting methods in order to facilitate the comparison of occupational respiratory PGM exposure results from different studies in future. In short, these recommendations include that personal exposure monitoring be conducted instead of area monitoring; that a variety of work areas and tasks be included in exposure assessments; that the chemical form of the particular PGM measured be reported and that authors report the areas where the measurements were collected, the number of measurements collected as well as the minimum, maximum and mean (arithmetic or geometric) values.

- *Recommendation 2:* Workers who were directly exposed to platinum compounds experienced significantly higher respiratory and dermal exposure to soluble platinum as well as urinary platinum excretion compared to indirectly exposed workers. Therefore, it

is recommended that when performing risk assessments and implementing exposure control measures, the emphasis should be placed on reducing the exposure of directly exposed workers, such as process operators in high exposure areas (concentrate handling, PGM separation, pulveriser and ignition and precious metals areas) and maintenance workers first, followed by indirectly exposed workers.

- *Recommendation 3:* Workers performing non-production activities such as security and laundry personnel were also exposed to quantifiable levels of soluble platinum and it is recommended that these workers not be excluded from risk assessments, exposure monitoring, training sessions and medical surveillance.

- *Recommendation 4:* In 1945, Hunter *et al.* (1945) recommended that the most effective manner in which soluble platinum sensitisation can be prevented is not to allow the complex platinum salts to enter the workplace atmosphere and that this could be achieved through effective exhaust ventilation. The local extraction ventilation systems at the concentrate handling and the crushing and ignition areas of the refineries in the present study was not functioning effectively because the extraction points were located too far from the exposure sources and they were not fitted with the correct hoods. Subsequently, there was visible airborne dust in these areas. It is recommended that the ventilation systems in these high exposure areas be upgraded in order to effectively capture the particles being emitted from the concentrators, mechanical sieves and crushers. All extraction points should be fitted with the appropriate hoods and be placed within the correct distance from the source of dust generation in order to increase the effectiveness of the extraction system. Alternatively, mobile extraction hoods with flexible ducting that can be moved closer to the emission source can be used to increase the effectiveness of the extraction system. Additionally, particulates were observed to be leaking into the workplace air from a bag filter unit, which was located inside the concentrate handling area of one of the refineries. The unit was used to remove the PGM-containing dust from the ventilation system for re-entry into the refining process. Although the filter bag unit cannot be placed outside the concentrate handling area due to security reasons, the filter should be cleaned or replaced on a regular basis (according to the manufacturer's specifications) in order to prevent PGM dust from re-entering the workplace air. Alternatively the filter bag unit could be replaced with a cyclone dust separator which does not require regular filter replacement.

- *Recommendation 5:* Other high exposure tasks that generated high concentrations of PGM containing airborne dust were bagging of platinum salts in the precious metals areas and the loading of the PGM concentrate into the reactors in the PGM separation areas. At the bagging area, it is recommended that the outlets be fitted with coupling devices that can transfer the platinum salts from the chute or outlet to the bags without creating airborne dust. These coupling devices can be manufactured from flexible material which can be manipulated to guide the PGM salts into the bags without liberating particles into the air. At the reactors, the mouth of the reactor can be fitted with a hopper to reduce spillages when pouring the PGM concentrate. The top of the hopper can be fitted with a lip extraction hood which is connected to the extraction ventilation system. The lip extraction hood can then remove any airborne dust which is generated by pouring the concentrate into the reactor, after which it can be transported to the air cleaning unit and recycled. Placement of the lip extraction underneath the workers hands will prevent the generated dust from settling on the hands of the operator and help to reduce dermal exposure, in addition to respiratory exposure.

- *Recommendation 6:* It is recommended that all local extraction ventilation systems be kept in a good working order and tested at least every 24 months as stipulated by Section 12 of the Hazardous Chemical Substances Regulations (DOL, 2017) in order to ensure that they are functioning optimally. The monitoring of the effective operation of these systems should also be included in the checklist of the operators and health and safety representatives. Once the system is out of order or not functioning properly, the operator or health and safety representatives should report defects so that they can be repaired within a reasonable time. Effective reporting of defects might reduce the time that the system is out of order.

- *Recommendation 7:* It is recommended that areas where high exposure tasks such as the scooping of wet platinum salt from glove boxes or the loading of PGM concentrate into reactors take place, be temporarily demarcated with danger tape while these tasks are taking place. This will prevent unauthorised workers from moving through these areas and becoming exposed unnecessarily. These areas should then also be cleaned by the operator before removing the cordon.

- *Recommendation 8:* The skin of some workers was visibly dirty and the transfer of contaminants from contaminated hands to the mouth, other anatomical areas or food is, therefore, possible. Additionally, detectable concentrations of soluble platinum was removed from the canteen door handles during surface wipe sampling (Chapter 5), which suggests that workers' hands are contaminated with low concentrations of soluble platinum when entering the canteen. It is recommended that personal hygiene such procedures such as proper hand washing are strictly enforced. Prior to entering the canteen during tea and lunch, workers should wash their hands and place their jackets and PPE on hooks outside the canteen. This will contribute to reducing the risk of the canteen being contaminated.

- *Recommendation 9:* In general, the housekeeping and personal hygiene practices in the refineries were of a good standard. However, surface wipe sampling did reveal contamination on some of the surfaces such as control room tables, railings and door handles (Chapter 5), which were handled without gloves. It is recommended that special attention should be given to areas where large quantities of dust are generated and that these areas are thoroughly cleaned at the end of every shift in order to prevent the accumulation of contaminants. Contaminated surfaces which workers come into contact with the most (i.e. table surfaces, hand rails, glove-boxes, PPE etc.) should be kept as clean as possible in order to reduce dermal exposure. General areas such as the canteen areas and health clinics should also be cleaned daily. Cleaners should be trained on the potential risks associated with cleaning as well as the appropriate cleaning procedures that should be used.

- *Recommendation 10:* The inside of one of the operator's gloves as well as the inside of rubber gloves at glove boxes was contaminated with soluble platinum which contributed to dermal exposure. Workers should take care not to contaminate the inside of gloves or other PPE as this will increase their dermal exposure. Additionally, care should also be taken to regularly clean the reusable PPE that is not washed in the laundry (e.g. hard hats) since wearing dirty PPE could lead to further exposure. Section 11 (2) (d) of the Hazardous Chemical Substances Regulations (DOL, 2017) stipulates that all PPE should be kept in a good condition and effective working order. This should also be included in the training programmes and workers should be trained how to correctly handle and clean contaminated PPE.

- *Recommendation 11:* The workers carried their respiratory protecting equipment (RPE), as well as their gloves with them at all times. During periods when workers were not required to wear RPE, the RPE was hung on the belts of the workers or around their necks where contamination from the workplace atmosphere could take place. It is recommended that the RPE and the gloves be placed in separate sealable plastic bags when not being worn in order to prevent contamination. The bag can then be worn around the waists of workers. Workers should be trained how to remove contaminated gloves correctly, as not to cause further contamination on the inside of the glove. Additionally, the gloves, the RPE and the bag should be cleaned regularly to prevent the accumulation of contaminants.

- *Recommendation 12:* Section 11 (6) (a) of the Hazardous Chemical Substances Regulations (DOL, 2017) requires the provision of adequate washing facilities which can be used by workers to maintained good personal hygiene and to reduce the spread of hazardous chemical substances. The workers should be provided with adequate skin cleansers which can be used to wash their hands and other contaminated areas following exposure. Soaps with a pH of 5.5, which is similar to the pH of the skin, can be provided for workers to wash with. Workers should be trained on the correct method to wash hands and the importance of good personal hygiene.

- *Recommendation 13:* The findings from the biological monitoring conducted during this study confirmed that spot urine tests can be used as an additional tool in exposure assessment. As was stated in Chapter 6 of this thesis, they can be used to identify workers who might have an increased platinum body burden as a result of factors such as of misuse of PPE or ingestion which cannot be determined with traditional exposure assessments. It is recommended that the analysis of workers' urinary platinum excretion through spot urine sampling be added to the annual medical surveillance procedures. The findings from Chapter 4 of this thesis indicated that urinary platinum excretion does not vary significantly during the short term and spot urine samples can, therefore, be collected in the morning when workers report for their medical surveillance. Although no biological exposure index exists for urinary platinum excretion, the results can be compared to baseline values as established when a workers is first employed. Chapters 4 to 6 of this thesis showed that the urinary platinum excretion of workers is influenced

by the number of years which workers are employed at the refineries. Baseline urine samples should be collected when workers are first employed and annually during the medical examinations. This could shed light on how platinum is absorbed into the body over the worker's time of employment. An increased urinary platinum excretion compared to previous values will alert medical and occupational hygiene personnel that a specific worker might be experiencing increased exposure to platinum compounds through inhalation, skin absorption or ingestion. Additionally, the collection of a data bank of urinary platinum excretion measurements for each worker might help shed light on the trends in the exposure of precious metals refinery workers to platinum compounds and the effectiveness of engineering, administrative and personal protection control measures. If this is not financially feasible, biological monitoring of platinum can be implemented for workers who are directly exposed to platinum compounds since they experience increased urinary platinum excretion compared to workers who are indirectly exposed (Chapter 4 and 5).

- *Recommendation 14:* The effectiveness of engineering, administrative controls as well as PPE is highly dependent on their correct use by workers (Geer *et al.,* 2007). Workers from the refineries undergo regular training on the health hazards associated with working with soluble platinum as well as on the control measures and procedures that will reduce their exposure. However, it was noted during the period in which the monitoring was conducted that information on the risk of dermal exposure to hazardous chemicals, methods which can be used to reduce dermal exposure and methods that can be used to improve their skin condition were not covered in detail in the training syllabus. It is, therefore, recommended that, as per Section 3 of the Hazardous Chemical Substances Regulations (DOL, 2017), detailed information on dermal exposure and skin health be added to the training syllabus of the refineries. Furthermore, the workers should be trained on the proper handling and use of potentially contaminated PPE. This should include procedures on the correct donning of clean PPE prior to the shift and doffing of contaminated PPE afterwards.

- *Recommendation 15:* In Chapter 5 of this thesis it was reported that surfaces in the refineries were contaminated with quantifiable levels of soluble platinum. In addition to the quantitative analysis of soluble platinum on wipes collected on surfaces within the refineries which can be expensive and time consuming, a colorimetric technique can be

used to identify surface contamination. This method involves wiping the surface which might be contaminated with soluble platinum with tissue paper or a cotton wipe and spraying it with a 1% sodium borohydride solution. If the solution turns black, it indicates that the surface is contaminated. This technique can be used by cleaners to confirm that surfaces are free of platinum compounds. If implemented, cleaners should be thoroughly trained on how to use the method and how to interpret the results of the test.

- *Recommendation 16:* Chapter 6 of this thesis revealed the effect that the correct use of PPE can have on the dermal exposure to platinum compounds. The implementation of strict procedures regarding the use of PPE on entry to high exposure areas such as the concentrate handling areas or during high exposure tasks are recommended in order to ensure the correct use of PPE. Chapter 6 also showed that the use of disposable coveralls significantly reduced the dermal exposure of workers. It is, therefore, recommended that workers who are directly exposed to platinum compounds wear disposable coveralls over their standard ploy-cotton overalls while performing high exposure tasks. Following the shift, the coverall can then be processed along with the refinery's waste instead of being washed in the laundry. This will prevent the contaminants from being transported to the laundry where laundry workers can be indirectly exposed.

- *Recommendation 17:* The precious metals refineries where the study was conducted held weekly "safety talks" where issues regarding health and safety in the plants were discussed. It is recommended that items such as the correct procedures to be followed during high exposure tasks, the correct donning, doffing and cleaning of PPE, personal hygiene and general skin health be added to these talks in order to keep workers informed and to motivate them to follow the correct procedures.

- *Recommendation 18:* It is recommended that dermal exposure sampling be added to the exposure monitoring programme of the precious metals refineries in order to monitor the risk of dermal absorption of platinum compounds and to evaluate the effectiveness of procedures and control measures implemented to control exposure. Dermal exposure sampling should be carried out in addition to the air monitoring which is conducted every 24 months as per Section 6 (2) (c) of the Hazardous Chemical Substances Regulations (DOL, 2017).

- *Recommendation 19:* Chapter 3 of this thesis revealed that only a few countries or organisations have classified soluble platinum compounds as sensitisers (respiratory or skin). It is recommended that countries or organisations that set occupational health and safety standards classify soluble platinum compounds as sensitisers in order to alert employers and workers of the risks associated with working with these compounds. Since soluble platinum has been shown to be a potent respiratory sensitiser (Heederik *et al.*, 2016) and most of the countries or organisations have classified soluble platinum compounds as respiratory sensitisers (HSE, 2011; DOL, 2017) (see Chapter 3) it is recommended that soluble platinum compounds be classified as primarily respiratory sensitisers.

7.3 Limitations

The following factors are recognised to have limited the assessment of occupational exposure to platinum to some degree:

- *Limitation 1:* During the study an external accredited pathology laboratory was used to determine the platinum content of urine samples. This was because the researchers did not have access to analytical instruments with the required sensitivity and no other options were available in South Africa. The detection limit of the procedure available for the analysis of urinary platinum was 0.1 µg/l. This is high compared to detection limits (0.009 µg/l) of other studies where the urinary platinum excretion of the general public are reported (CDC, 2017). The detection limit of 0.1 µg/l, therefore, allowed for the investigation of the urinary platinum excretion of occupationally exposed persons but not of environmentally exposed persons since the urinary platinum excretion of the general public is usually below 0.05 µg/l (CDC, 2017). Subsequently, the urinary platinum excretion of the non-occupationally exposed control group in Chapter 4 was below the limit of detection. Access to more sensitive analytical procedures would have allowed for a more detailed analysis of the urinary platinum excretion of the group of workers which were indirectly exposed to platinum compounds as well as the control group.

- *Limitation 2:* No international accepted dermal exposure assessment methods exist for platinum compounds and the recovery and wipe efficiencies of Ghostwipes™ for soluble platinum was, therefore, evaluated (Chapter 5). The evaluation of the wipe efficiency of Ghostwipes™ for soluble platinum was evaluated using glass plates. This procedure was similar to the procedure reported in the Occupational Safety and Health

Administration's (OSHA) ID-125G method (OSHA, 2002), where the surface wipe efficiency of Ghostwipes™ for other metals such as nickel, lead and cobalt on glass plates was evaluated. The surface of the skin is uneven and rough compared to a glass surface. Since the Ghostwipes™ are not validated for rough, uneven surfaces, it is possible that the concentration of soluble platinum present on the skin of workers were underestimated because the contaminant present in the folds of the skin were potentially not removed by the wipe. Day *et al.* (2009) also listed the possible underestimation of dermal exposure results from skin wipe sampling as a limitation during their assessments. Irrespective of this limitation, the skin wipe sampling conducted during this study still showed that concentrations of soluble platinum are present on the skin of precious metals refinery workers.

- *Limitation 3:* The effect of ingestion on the urinary platinum excretion of workers was not accounted for during the study since the absorption of platinum compounds from ingestion is low (Gad, 2005; Wiseman and Zereini, 2009). Animal studies with rats have demonstrated that less than 1% of platinum is absorbed by the gastrointestinal tract following oral dosing (Moore *et al.*, 1975). However, soluble platinum contamination was measured on the palms and wrists of workers and the transfer of contaminants was observed to occur from the hands of workers to their necks and foreheads. It is, therefore, plausible that the same type of transfer will occur as a result of hand-to-mouth contact as discussed by Gorman Ng *et al*. (2016) who reported that hand-to-mouth contact occurred on average 6.3 times per hour in various industries. Consequently, it is possible that ingestion could have contributed to the platinum body burden of workers to some degree although this contribution is expected to be extremely low.

- *Limitation 4:* Stefaniak *et al.* (2014) stated that the use of reactant-assisted analytical chemistry to quantify the mass of metals on dermal exposure samples could lead to an over-estimation of biologically relevant exposure due to the reactants not being representative of the skin surface film liquids. Since no standard dermal exposure assessment and analysis methodology was available for soluble platinum, the samples were analysed using the Methods for the Determination of Hazardous Substances (MDHS) 46/2 method which is used to analyse for soluble platinum in air (HSE, 1996). This method involves leaching the soluble platinum fraction with 0.07 M hydrochloric acid and states that microgram amounts of soluble platinum should be approximately as

soluble in the 0.07 M hydrochloric solution as it will be in water. Nevertheless, the possibility exists that the mass of bioaccessible soluble platinum was overestimated.

- *Limitation 5:* Day *et al.* (2009) and Du Plessis *et al.* (2010) both reported that detectable levels of metals (nickel, cobalt and chromium) were present on the skin of workers before the start of their shifts. Pre-shift dermal exposure samples were not included in the present study because the aim of this study was to assess occupational dermal exposure to platinum. Therefore, the focus was placed on the dermal exposure of workers during the shift. Additionally, some financial constraints were also involved in establishing this approach. If included, the results could have provided some additional information on the personal hygiene practices of workers.

7.4 Future studies

Following the completion of this thesis, several opportunities for possible future studies have been identified. These future studies include the following:

- Franken *et al*. (2014) demonstrated during *in vitro* skin permeation experiments that most of the soluble platinum deposited onto the skin was retained inside the skin to form a reservoir which could become systemically available with time. Chapter 5 of this thesis demonstrated that there were soluble platinum present on the skin of precious metal refinery workers which could potentially permeate through the skin. By making use of tape stripping, the concentrations of soluble platinum present in the various layers of the skin could be quantified. The confirmation of a soluble platinum reservoir in different layers of the skin of workers could provide more clarity on the importance of the skin as a route of exposure for soluble platinum.

- The refining of PGMs involves the use of a variety of irritant chemicals such as chlorine, hydrochloric acid and aqua regia to which precious metals refinery workers can potentially be exposed to (Seymour and O'Farrelly, 2012). Exposure to these irritants could lead to degradation of the skin barrier and increase permeation of chemicals, such as PGMs, through the skin (Kezic and Nielsen, 2009). Decreased skin barrier function has been reported for base metals refineries (Du Plessis *et al.*, 2010). Future studies could include the evaluation of the skin barrier function of precious metals refinery workers in order to identify if working in the refinery environment could possibly lead to

impaired skin barrier function and the subsequent increased risk for permeation of chemicals through the skin.

- Occupational exposure to soluble platinum is associated with diseases of the respiratory tract and the skin (Hunter *et al*., 1945; Merget *et al*., 2000). The role of respiratory exposure in the development of soluble platinum sensitisation has been investigated (Heederik *et al*., 2017) but the role of dermal exposure in the development of sensitisation, as was suggested by Maynard *et al*. (1997), is still unclear. Chapter 5 of this thesis confirmed the presence of soluble platinum on the skin of precious metals refinery workers and showed that a positive relationship exists between dermal exposure and platinum body burden. Future studies could include investigating the role of dermal exposure to soluble platinum in the development of respiratory sensitisation and skin diseases such as contact dermatitis, urticaria and eczema.

- Recommendations on the control and reduction of exposure to platinum compounds (Section 7.2) have been made to the respective precious metals refineries included in this study. Following the implementation of these recommendations the re-assessment of the workers' respiratory and dermal exposure as well as their urinary platinum excretion will prove useful in assessing the effectiveness of the implemented control measures.

- The present study, which was performed in precious metals refineries, could be conducted at secondary platinum industries such as automotive catalyst production plants where workers are also exposed to soluble platinum compounds. This could be done in order to establish whether the same degree of correlations exist between exposure routes and platinum body burden.

- Acid wipe sampling has been successfully used to assess dermal exposure to nickel, chromium and cobalt (Lidén *et al*., 2006). The potential of the acid wipe sampling method, which utilises cellulose wipes wetted with a 1% nitric acid solution, to assess dermal exposure to soluble platinum could also be investigated.

- As discussed in Section 7.3 in this chapter, the contribution of ingestion as an exposure route was not considered during this study. Future studies could include a combination of dermal wipe sampling of the peri-oral region, and hand-to-mouth and object-to-mouth

behaviour among precious metals refinery workers in order to investigate the risk for inadvertent ingestion of platinum compounds.

- This study collected pre-shift spot urine samples. Wang *et al.* (2016) analysed the metal content (arsenic, cadmium, cobalt, copper, lead, molybdenum and nickel) in spot, first morning and 24 hour urine samples over a three month period and suggested that it is more valuable to collect a high number of measurements from each participant in order to estimate a participant-specific mean than to collect 24 hour or first morning samples. Future studies might include the characterisation of the urinary platinum excretion of workers in order to examine the variation in workers' urinary platinum excretion over time.

- None of the workers who participated in this study were sensitised to soluble platinum. Future studies might involve the measurement of the urinary platinum excretion of workers who are already sensitised to soluble platinum in order to determine the platinum body burden of those workers.

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APPENDIX B

Proof of submission of articles II and III to scientific journal

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11-Oct-2017
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Article III

04-Dec-2017

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APPENDIX C

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2017-12-04

I, Jannetje Levina De Kock hereby declare that the thesis

Occupational exposure to platinum at South African precious metals refineries

by
SJ L Linde

for submission to the NWU

- has been edited for language correctness and spelling.
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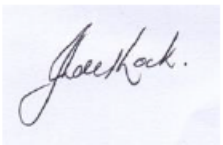

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