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

# Evaluation of exposure to airborne soluble platinum in a precious metal refinery during non-routine operations


## A. VOS (Hons. B.Sc Physiology)


**Mini-dissertation submitted in partial fulfilment of the requirements for the degree *Magister Scientia* in Occupational Hygiene at the Potchefstroom Campus of the North-West University**


**Supervisor:** **Mr. PJ Laubscher**

**Co-supervisors:** **Dr. JL Du Plessis**
**Dr. CJ Badenhorst**


**February 2012**

## ACKNOWLEDGEMENTS

I would like to thank the many people and organisations, whose help made this project possible:

- My supervisor, Mr. PJ Laubscher, North-West University, Potchefstroom Campus, for his guidance, assistance and continuous encouragement throughout the planning and execution of the research project.

- Dr. JL du Plessis, my assistant project leader, for technical advice and input during the writing of the mini-dissertation.

- Dr. Suria Ellis, of the Statistical Consulting Services of the North-West University, Potchefstroom Campus, for the statistical analysis of the data and assistance with the interpretation of the statistical results.

- Anglo Platinum, for financial support and arrangements to carry out measurements.

- Dr. C Badenhorst, Anglo platinum, group occupational hygiene specialist, for his expertise, assistance with protocol, support and sourcing of the research project.

- Ms. Corli Venter for her valuable time, assistance and support during the scheduling and collection of the sampling data.

- The refinery workers who participated in the study, for their enthusiasm and exceptional co-operation during the research project.

- Prof. Lesley Greyvenstein for the language editing.

- My family and friends for their love, support and non-stop encouragement to complete my dissertation.

- All the glory to my Heavenly Father for His unconditional love, everlasting truthfulness and caring guidance throughout this study and throughout my journey in this life, thank you Father.

# TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AAS** | Atomic absorption spectrometry |
| **ACGIH** | American Conference of Industrial Hygienists |
| **AES** | Atomic emission spectrometry |
| **AIHA** | American Industrial Hygiene Association |
| **$Al_2O_3$/Pt** | Aluminium oxide particles ≤ 5 µm (mean: 1.3 µm) onto which platinum particles ≥ 4 nm were deposited |
| **AV** | Adsorptive Voltammetry |
| **BAL** | Bronchoalveolar lavage |
| **bw** | Body weight |
| **CAS** | Chemical Abstracts Service number |
| **CEN** | Comité Européen de Normalization |
| **CFE** | Colony-forming efficiency |
| **$Cl_2$/HCl** | Concentrated hydrochloric acid through which chlorine gas is bubbled |
| **DECOS** | Dutch Expert Committee on Occupational Standards |
| **DNA** | Deoxyribonucleic acid |
| **dw** | Dry weight |
| **$EC_{50}$** | 50% inhibition of cell growth |
| **EEC** | European Economic Community |
| **EINECS** | European Inventory of Existing Chemical Substances |
| **EPA** | Environmental Protection Agency |
| **EU** | European Union |
| **$FEF_{25}$** | Forced expiratory flow at 25% of vital capacity |
| **$FEV_1$** | Forced expiratory volume in one second |
| **$FEV_{0.5}$** | Forced expiratory volume in 0.5 second |
| **FISH** | Fluorescence *in situ* hybridisation |
| **FVC** | Forced vital capacity |
| **GFAAS** | Graphite Furnace Atomic Absorption Spectrometry |
| **HLA** | Human leukocyte-associated antigen |
| **HSE** | Health and Safety Executive |
| **ICP-MS** | Inductively Coupled Plasma Mass Spectrometry |
| **IgE** | Immunoglobulin E |
| **IL** | Interleukin |
| **IOM** | Institute of Occupational Medicine |
| **IPCS** | International Programme on Chemical Safety |

| | |
|---|---|
| **$LD_{25}$** | Dose that is estimated to be lethal to 25% of test animals |
| **$LD_{50}$** | Dose that is estimated to be lethal to 50% of test animals |
| **MCE** | Mixed Cellulose Ester |
| **MDHS** | Method for the Determination of Hazardous Substances |
| **MEL** | Maximum exposure limit |
| **MMAD** | Mass median aerodynamic diameter |
| **NHANES** | National Health and Nutrition Examination Survey |
| **NIOSH** | National Institute for Occupational Safety and Health |
| **OEL** | Occupational exposure limit |
| **OES** | Occupational exposure standard |
| **OESSM** | Occupational Exposure Sampling Strategy Manual |
| **OSHA** | Occupational Safety and Health Administration |
| **PBMC** | Peripheral blood mononuclear cells |
| **PGMs** | Platinum Group Metals |
| **pH** | Potential of Hydrogen. The logarithm of the reciprocal of hydrogen-ion concentration in gram atoms per litre; provides a measure on a scale from 0 to 14 of the acidity or alkalinity of a solution (7 = neutral, > 7 = basic, < 7 acidic). |
| **$PM_{10}$** | Concentrations of airborne particulate matter less than 10 micrometers in diameter |
| **PSS** | Platinum Salt Sensitisation |
| **Pt** | Platinum |
| **$^{191}Pt$** | Radiolabelled platinum |
| **$PtAs_2$** | Sperrylite |
| **(Pt,Pd,Ni)S** | Braggite |
| **(Pt,Pd)S** | Cooperite |
| **$R_L$** | Pulmonary flow resistance |
| **RTECS** | Registry of Toxic Effects of Chemical Substances |
| **Stock Take** | Systematic disassembling and cleaning of plant equipment and the accounting for stock during this period |
| **TCR** | T-cell receptor |
| **TLV** | Threshold limit value |
| **TLV-TWA** | Threshold Limit Value-Time-Weighted Average |
| **TWA** | Time-weighted average |
| **WHO** | World Health Organisation |

## STANDARD UNITS

| | |
|---|---|
| **°C** | Degrees Celsius |
| **g** | Grams |
| **h** | Hour |
| **kg** | Kilogram |
| **km** | Kilometre |
| **kU** | Kilo unit |
| **L** | Litre |
| **M** | Molar |
| **$m^3$** | Cubic meter |
| **mCi** | Millicurie |
| **mg** | Milligram |
| **min** | Minute |
| **mL** | Millilitre |
| **mm** | Millimetre |
| **mM** | Millimolar |
| **ng** | Nanogram |
| **nm** | Nanometre |
| **pg** | Picogram |
| **ppm** | Parts per million |
| **µg** | Microgram |
| **µm** | Micrometers |

**AFRIKAANSE TITEL: Evaluering van die blootstelling aan luggedraagde oplosbare platinum in 'n edelmetaal-raffinadery tydens nie-roetine-bedrywighede.**

## OPSOMMING

**Agtergrond:** Platinum-raffinadery werkers word blootgestel aan verskeie elemente gedurende die raffineringsproses, waarvan oplosbare platinumsoute ón potensiële gesondheidsrisiko inhou. Platinumsoute is uiters potente sensiteerders wat die kliniese sindroom van platinumsout sensitiwiteit tot gevolg kan hê en kan lei tot vel en respiratoriese hipersensitiwiteit in raffinadery werkers. Verskeie gepubliseerde navorsingsartikels dokumenteer raffinadery werkers se blootstellingsvlakke aan oplosbare platinumsoute tydens produksie. Nietemin is die blootstellingsvlakke van oplosbare platinumsoute tydens nie-roetine voorraadopnames onbekend, hoewel gevalle van sensitisering gediagnoseer is na nie-operasionele periodes. Die voorraadopname vir die platinum-raffinadery wat bestudeer is het 18 Januarie 2010 begin en 22 Februarie 2010 geëindig. Groter klem is geplaas op die skoonmaak en uitspoel van die raffinadery se toerusting eerder as op die oopmaak daarvan. Die doel was om net 10% van die toerusting wat voorheen oopgemaak is oop te maak om sodoende die blootstellingsrisiko van werkers aan platinumsoute te verlaag, om potensiële beskadiging van toerusting te verminder en vir koste en tyd besparings doeleindes.

**Doel:** Hierdie studie het die volgende ten doel:

(i) kwantifisering van werkarea en persoonlike blootstellingsvlakke;

(ii) identifisering van werkareas en take met blootstellingsvlakke bo die beroepsblootstellings-drempel ($\geq$2 µg/m$^3$);

(iii) bepaling van betekenisvolheid van verskille tussen die:

  a) persoonlike moniteringsgroepe (ingenieurs teenoor produksie),

  b) area moniteringsgroepe (oop teenoor geslote-gesig monitering),

  c) werkareas,

  d) totale area en totale persoonlike moniteringsgroepe en die

(iv) evaluering van die doeltreffendheid van die bestaande beheermaatreëls.

**Ontwerp en Metode:** 'n Totaal van 58 platinum monsters is versamel, wat bestaan uit 38 persoonlike en 20 area monsters. Persoonlike monsterneming is gedoen met IOM monster-nemers met herbruikbare 25 mm filterhouers wat gemengde sellulose-ester membraan filters bevat het vir die versameling van inasembare partikels. Omdat beide die kasset en filter voor en na metings as 'n eenheid geweeg word, is al die versamelde deeltjies (selfs die wat teen die kante van die monsternemer vassit) in die analise ingesluit.

Monitering is uitgevoer in ooreenstemming met die voorraadopname skedule en omvang en het ón rooster ingesluit vir die sistematiese oopmaak en skoonmaak van die raffinadery volgens die proses vloei. ón Teikengroep van maksimum vyf passers en vyf operateurs per area is geïdentifiseer, wat onderskeidelik verantwoordelik was vir die oopmaak en skoonmaak van die toerusting. Die moniteringstrategie vir hierdie studie is gebaseer op die identifisering en monitering van werknemers wat vermoedelik die hoogste blootstellingsrisiko het. Die ñOccupational Exposure Sampling Strategy Manualò (OESSM) verwys daarna as die ñmaksimum risiko werknemersò (Liedel *et al.*, 1977). Seleksie van die maksimum risiko werknemers is met redelike sekerheid gedoen aangesien die werknemers naaste aan die bron van blootstelling gemeet is. Monitering is uitgevoer vir die totale tydsduur van die taak en het ón enkele meting verteenwoordig.

Area monitering het die gebruik van BUCKAir hoëvolume pompe ingesluit toegerus met ón herbruikbare 47 mm filterhouer wat 'n gemengde sellulose-ester membraan filter bevat om die verspreiding van die kontaminant in die werkplek te meet. Die hoëvolume pompe is gekalibreer om teen 'n vloeisnelheid van 20 L/min te meet. Die filterhouer is 1.5 m van die grondoppervlak geposisioneer en so na as moontlik aan die werksarea. Indien dit nie moontlik was nie is die filterhouer so na as moontlik aan die blootstellingsbron geplaas. Monsters is versamel en ontleed volgens die metode vir die bepaling van gevaarlike stowwe 46/2 (MDHS 46/2). Dit is 'n gevorderde moniterings en analise standaard wat in staat is om lae konsentrasies oplosbare platinum op te spoor (0.01 µg/m$^3$).

**Resultate:** 38 persoonlike platinummonsters is versamel en sluit ingenieurs (n=15) en produksie (n=23) moniteringsgroepe in. 21% van die persoonlike platinum blootstellingsvlakke (n=38) het die beroepsblootstellingsdrempel van 2 µg/m$^3$ oorskry en het gewissel tussen 0.004-20.479 µg/m$^3$. 20 area platinummonsters is versamel en sluit oop (n=10) en geslote-gesig monsternemer (n=10) moniteringsgroepe in. 10% van die area platinum konsentrasie vlakke (n=20) het die beroepsblootstellingsdrempel van 2 µg/m$^3$ oorskry en het gewissel tussen 0.0004-5.752 µg/m$^3$. Die gemiddelde persoonlike blootstellingsvlakke vir die produksie moniteringsgroep (2.739 µg/m$^3$) was betekenisvol hoër (p=0.033) in vergelyking met die ingenieur se gemiddelde persoonlike blootstellingsvlakke (0.393 µg/m$^3$). Die hoër blootstellingsvlakke was geantisipeer omdat die produksie personeel meer direk blootgestel was tydens die skoonmaak en uitspoel van die raffinadery se toerusting in vergelyking met die ingenieurspersoneel wat alleenlik betrokke was by die oopmaak van die toerusting.

Alhoewel die gemiddelde area blootstellingsvlakke vir die oop-gesig monitering (0.725 µg/m$^3$) hoër was as die geslote-gesig monitering (0.441 µg/m$^3$) was geen betekenisvolle verskil aangedui nie (p=0.579). Die gemiddelde area blootstellingsvlakke (0.583 µg/m$^3$) was betekenisvol laer (p=0.004) as die gemiddelde persoonlike blootstellingsvlakke (1.813 µg/m$^3$) vir dieselde werksareas en take en is sodoende nie ón doeltreffende indikator van persoonlike blootstellingsvlakke nie. Hoër persoonlike blootstellingsvlakke was geantisipeer omrede die werkers nader aan die blootstellingsbron was en platinumsoute versprei en verdun in die lug van die werkplek met ón gevolglike laer area blootstellingsvlak.

**Gevolgtrekking:** Die navorsingstudie het die probleemstelling aangespreek, die doelwitte bereik soos uiteengesit in Hoofstuk 1, hipoteses is aanvaar en verwerp en toekomstige studies is aanbeveel.

Hipoteses in die studie gestel:

a) Raffinadery werkers word blootgestel aan oplosbare platinumsoute gedurende nie-operasionele periodes;
b) Persoonlike blootstellingsvlakke verskil nie betekenisvol tussen die ingenieurs en produksie moniteringsgroepe nie;
c) Area blootstellingsvlakke verskil nie betekenisvol tussen die oop en geslote-gesig moniteringsgroepe nie;
d) Blootstellingsvlakke verskil nie betekenisvol tussen die werksareas nie;
e) Blootstellingsvlakke tussen die totale area en totale persoonlike moniteringsgroepe verskil betekenisvol.

Die resultate het aangedui dat platinum-raffinadery werkers blootgestel word aan oplosbare platinumsoute gedurende nie-operasionele periodes en hipotese a is aanvaar. Die persoonlike blootstellingsvlakke van die ingenieurs en produksie moniteringsgroepe het betekenisvol van mekaar verskil (p=0.033) en hipotese b is verwerp. Area blootstellingsvlakke het nie betekenisvol verskil (p=0.579) tussen die oop en geslote-gesig moniteringsgroepe nie en hipotese c is aanvaar. Geen betekenisvolle verskille (p>0.05) is gevind tussen die werksareas nie en hipotese d is aanvaar. Blootstellingsvlakke tussen die totale area en totale persoonlike moniteringsgroepe verskil betekenisvol (p=0.004) en hipotese d is aanvaar.

**Sleutelwoorde:** platinum-raffinadery, nie-operasionele periode, blootstellingsvlakke, platinum, platinumsout sensitisering

**ENGLISH TITLE: Evaluation of exposure to airborne soluble platinum in a precious metal refinery during non-routine operations.**

**SUMMARY**

**Background:** Platinum refinery workers are exposed to various elements during the refining process, with soluble platinum salts posing a potential health risk. Platinum salts are extremely potent sensitisers that can result in the clinical syndrome of platinum salt sensitivity (PSS) that leads to skin and respiratory hypersensitivity in refinery workers. Several published research articles document refinery workersôexposure levels to soluble platinum salts during production. However, the exposure levels to soluble platinum salts during non-routine stock take activities are unknown although cases of sensitisation have been diagnosed following these non-operational periods. Stock take for the platinum refinery under study commenced on 18 January 2010 and ended 22 February 2010. Increased emphasis was placed on flushing plant equipment rather than dismantling it. The aim was to dismantle 10% of what previously was dismantled to reduce the risk of exposing employees to soluble platinum salts, to reduce the chance of damaging plant equipment and for cost and time saving purposes.

**Aim:** The objectives of this study are to:

(i) quantify work area and personal exposure levels;

(ii) identify work areas and work practices with exposure levels exceeding the occupational exposure limit (OEL) ($\geq$2 μg/m$^3$);

(iii) determine whether exposure levels differ significantly between:
   a) personal sampling groups (engineering versus production),
   b) area sampling groups (open versus closed-face sampling),
   c) work areas,
   d) total area and total personal sampling groups and to

(iv) evaluate the efficiency of the current control measures utilised.

**Design and Method:** A total of 58 platinum samples were collected, consisting of 38 personal and 20 area samples. Personal sampling consisted of Institute of Occupational Medicine (IOM) samplers housing reusable 25 mm filter cassettes with mixed cellulose ester (MCE) membrane filters for the collection of inhalable airborne particles. Because both the cassette and the filter were pre and post-weighed as a single unit, all particles collected (even those against the walls of the cassette) were included in the analysis. Sampling was conducted in accordance with the stock take schedule and scope and included a roster for the systematic dismantling and cleaning of the refinery, following the process flow.

A target population of maximum five fitters and five operators per area were identified, responsible for dismantling and cleaning plant equipment respectively. The sampling strategy was based on the identification and sampling of employees presumed to have the highest exposure risk. The Occupational Exposure Sampling Strategy Manual (OESSM) refers to this as the ñmaximum risk employeesò (Liedel *et al*., 1977). The selection of the maximum risk employees was done with reasonable certainty since the employees sampled were working closest to the source of exposure. Sampling was conducted for the total duration of the task consisting of single sample measurements.

Area sampling was conducted by means of BUCKAir high volume samplers fitted with pre-weighed 47 mm MCE filter cassettes to show the spread of the contaminant in the work area. The high volume samplers were calibrated to operate at a sampling volume of 20 L/min. The sampling heads were positioned 1.5 m from the ground surface and as near as possible to the work location or failing this as near as is possible to major sources of exposure. Samples were collected and analysed according to the method for the determination of hazardous substances 46/2 (MDHS 46/2). This is an advanced sampling and analysis standard which enables detection of low levels of soluble platinum (0.01 µg/m$^3$).

**Results:** Thirty eight personal platinum samples were collected, consisting of a sampled engineering (n=15) and production (n=23) subgroup. Out of the thirty eight personal samples taken in total, 21% of the samplesô concentrations exceeded the OEL of 2 µg/m$^3$ and ranged between 0.004-20.479 µg/m$^3$. Twenty area platinum samples were collected, consisting of open (n=10) and closed face (n=10) sampling. Out of the twenty area samples taken in total, 10% of the samplesô concentrations exceeded the OEL of 2 µg/m$^3$ and ranged between 0.0004-5.752 µg/m$^3$. The mean personal exposure levels for the production subgroup (2.739 µg/m$^3$) were significantly higher compared to the engineering subgroupôs mean personal exposure levels (0.393 µg/m$^3$). This significant difference (p=0.033) was expected since the production subgroup was more exposed and involved in the digging out of residues and the cleaning of plant equipment compared to the engineering subgroup with limited exposure and involved in the opening of plant equipment. Although the mean exposure levels for open face sampling (0.725 µg/m$^3$) were higher compared to the mean exposure levels for closed face sampling (0.441 µg/m$^3$) no significant difference (p=0.579) were noted. The mean area exposure levels (0.583 µg/m$^3$) were significantly lower (p=0.004) compared to the mean personal exposure levels (1.813 µg/m$^3$) for similar areas and tasks performed and, therefore, not an effective indicator of personal exposure levels.

Higher personal exposure levels were expected since the workers were closer to the source of exposure and since the platinum salts could have diluted in the workplaceôs air resulting in lower area exposure levels.

**Conclusion:** The research study addressed the problem statement, met the objectives set out in Chapter 1, hypotheses were accepted and rejected and future studies were recommended.

It was hypothesised that:

a) refinery workers are exposed to airborne soluble platinum during non-operational periods;
b) exposure levels do not differ significantly between the personal sampling groups (engineering vs production);
c) exposure levels do not differ significantly between the area sampling groups (open versus closed-face sampling);
d) exposure levels do not differ significantly between work areas;
e) exposure levels differ significantly between total personal and total area sampling groups.

The results confirmed that refinery workers are exposed to airborne soluble platinum during non-operational periods and hypothesis a was accepted. The personal exposure levels of the engineering versus production sampling groups differed statistically ($p=0.033$) and hypothesis b was rejected. The exposure levels of the open and closed face sampling groups did not differ significantly ($p=0.579$) and hypothesis c was accepted. In addition no statistical difference ($p>0.05$) was indicated between the work areas and hypothesis d was accepted. Total personal versus total area exposure levels ($p=0.004$) differed statistically and hypothesis e was accepted.

**Keywords:** platinum refinery, non-operational period, exposure levels, platinum, platinum salt sensitisation

## PREFACE

This mini-dissertation is presented for the partial completion of the M.Sc. degree in Occupational Hygiene at the North-West University, Potchefstroom. It was decided to use the article format for the purpose of this study. Therefore, Chapter 3 is a manuscript in the form of an article. The article will be submitted for publication to the accredited journal, Annals of Occupational Hygiene. Although the appropriate and relevant literature background is discussed in the manuscript, Chapter 1 also gives an additional, more elaborate literature background. In the manuscript the project leader and assistant project leader are named as co-authors. The main and first author was, however, responsible for most stages of the manuscript, including literature searches, the collection of data, interpretation of results and writing of the article. The co-authors, therefore, acted in their roles as project leader and assistant project leader. All co-authors gave consent that the article could be used in this mini-dissertation. In Chapter 4 a summary of the main findings is provided, confounders are discussed, conclusions are drawn and recommendations are made. The relevant references are provided according to the authors' instructions provided by the journal, Annals of Occupational Hygiene. For the purpose of uniformity, the same style of reference was used throughout this mini-dissertation.

## AUTHORS' CONTRIBUTIONS

The contribution of each of the researchers who participated in the planning and execution of this study is outlined below.

**Contributors and their respective roles**

| Name | Contribution |
|---|---|
| Mrs. A. Vos: Principal researcher | Researching relevant literature, collection of data, interpreting results, planning, design and writing of mini-dissertation. |
| Mr. P.J. Laubscher: Supervisor | Assisting with the design and planning of the study, approval of title and protocol, reviewing of the results and advising on the interpretation of results. |
| Dr. J.L. Du Plessis: Co-supervisors | Technical advice during the writing of the mini-dissertation. |
| Dr. C.J. Badenhorst: Co-supervisors | Assisting with the approval, sourcing and planning of the research project. |

The declaration below confirms each of the contributors' individual role in this study:

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

_____ _____

Mr. P.J. Laubscher Dr. J.L. Du Plessis

_____

Dr. C.J. Badenhorst

# CHAPTER 1: INTRODUCTION

## 1.1 GENERAL INTRODUCTION

Platinum mining in South Africa has experienced a significant growth over the past 10 years, making the country the largest platinum producer in the world (Boshoff, 2000). Although seen as a positive trend this goes hand in hand with increased occupational related diseases. Consequently, it can and does lead to legislation that makes mining more expensive. The Mine Health and Safety Act (29/1996), Occupational Health and Safety Act (85/1993), and the Hazardous Chemical Substance Regulations (R.1179/1995) all relate to the health and safety of workers and the public in industrial and private sectors.

There are three primary categories of industrial sources that result in occupational exposure to platinum: mining, refining and processing. Platinum in the mining operation usually is found in the insoluble form, (platinum metal) and is considered to be non-toxic. The refining operations provide predominantly the soluble forms of platinum namely chlorinated platinum salts that pose significant health risks. The main occupational exposure to chlorinated platinum salts occurs in primary and secondary refining of platinum. The increased production of finely divided metal powders from chlorinated platinum salts has led to the increased handling of these salts in the precious metals industry (Johnson *et al.*, 1975; Health Council of the Netherlands, 2008).

The most significant health risk from occupational exposure to soluble platinum compounds results in skin and respiratory irritations and, if prolonged, to asthma and severe respiratory distress. It is during the production and handling of chlorinated platinum salts (complex halogenated salts and hexachloroplatinic acid) that allergic symptoms have occurred. Elicitation of allergic symptoms normally occurs at platinum air levels below 2 $\mu g/m^3$, but cases have been reported where sensitisation occurred at platinum levels as low as 0.05 $\mu g/m^3$ (WHO, 2000; Health Council of the Netherlands, 2008).

Because the correlation between platinum exposure levels and sensitisation is unknown, the World Health Organisation (WHO) task group considered that a recommendation for a reduction in the OEL cannot at present be justified. They did, however, recommend that the OEL of 2 $\mu g/m^3$ be changed from an 8-hour time-weighted average (TWA) to a ceiling value, and that personal sampling devices be used in conjunction with area sampling to determine more correctly the true platinum exposure.

Should it be established that sensitisation has occurred consistently at platinum levels below the current OEL of 2 μg/m$^3$, and that intermittent, short exposures above this level had not taken place, there would be strong grounds for reducing the OEL (WHO, 1991, 2000). Most countries with platinum industry activity impose low limits for workplace chemical exposure namely an 8-hour TWA exposure limit of 2 μg/m$^3$ for water-soluble species of platinum. Even so, this OEL alone is not completely protective and sensitisation can and has occurred despite consistent compliance with this limit (WHO, 2000; Bullock, 2010). Even in current, well-controlled working environments, about 40 (1%) out of 4000 workers exposed worldwide to chlorinated platinum salts, are sensitised annually, leading to their permanent removal from any possible exposure, and thus often removal from employment within the platinum industry (Bullock, 2010).

As a matter of social justice, significant human suffering related to work is unacceptable. Ramazzini said, about 300 years ago: ñIt is but a sad profit which is achieved at the cost of the health of workers...ò Moreover, appreciable financial losses result from the burden of occupational and work related diseases on national health and social security systems, as well as from their negative influence on production and quality of products (WHO, 1999). Great humanitarian and monetary costs are experienced by individuals due to a loss of income and medical or related expenses; and by mining companies through the loss of experienced employees and the expense of recruiting and training new employees, direct medical expenses and compensation levies (Calverley and Murray, 2005). People should not have to endure, and countries cannot afford, such damaging effects (Goelzer, 1996).

All these adverse consequences, which are economically costly to employers and to society, are preventable through measures which have been known for a long time, and which are often of low cost. One of the preventable measures that can be performed at minimal cost, includes quantitative evaluations of airborne dust in the workplace to assess workersô exposure in relation to an adopted standard, to determine whether the contamination represents a potential or a real hazard, and to establish the need for control measures or to assess the effectiveness of control strategies (WHO, 1999).

Several studies (Fothergill *et al.,* 1945; Hunter *et al.*, 1945; Johnson *et al.*, 1976; Shi, 1987; Merget *et al.*, 1988; Baker *et al.*, 1990; Bolm-Audorff *et al., 1992*; HSE, 1996) documented refinery workersô exposure levels to soluble platinum salts during production but none were documented for non-routine stock take activities, although cases of sensitisation previously have been diagnosed following these non-operational periods at the precious metals refinery under study.

This led to the following questions:

a) What are the soluble platinum exposure levels during non-operational periods?
b) Will the obtained exposure levels exceed the current OEL?
c) Do these levels represent a potential or a real hazard?
d) Do the current control measures offer adequate protection?

These questions led to the need for this research. The main goal of the study is to quantify occupational exposure of workers to soluble platinum during non-operational periods, utilising both personal and area sampling as recommended by the WHO task group.

## 1.2 PRESENT STUDY

### 1.2.1 Problem Statement

A number of studies have provided clear evidence that exposure to soluble platinum salts during the refining process leads to occupational skin and respiratory hypersensitivity in humans. Exposure levels during production periods have been monitored and documented, however the extent of exposure during non-routine stock take activities is unknown although cases of sensitisaton have been reported following these non-operational periods. Therefore, quantitative exposure measurements during these non-operational periods are neccesary in order to determine exposure levels, to comply legally and to control all risks involved.

### 1.2.2 Objectives of the study

The objectives of this study were to:

a) quantify area and personal exposure levels during non-operational periods;
b) identify areas and tasks that result in exposure levels exceeding the OEL ($\geq$ 2 µg/m$^3$);
c) determine whether the exposure levels differ significantly between the personal sampling groups (engineering versus production),
d) between the static sampling groups (open versus closed-face sampling),
e) between work areas,
f) between total personal and total area sampling to evaluate the effectiveness of area monitoring as a possible indicator of personal exposure levels and to
g) investigate the efficiency of the current control measures utilised.

### 1.2.3 Hypotheses

It is proposed that:

a) refinery workers are exposed to airborne soluble platinum during non-operational periods;
b) exposure levels do not differ significantly between the personal sampling groups (engineering versus production);
c) exposure levels do not differ significantly between the area sampling groups (open versus closed-face sampling);
d) exposure levels do not differ significantly between work areas;
e) exposure levels differ significantly between total personal and total static sampling groups.

### 1.2.4 Construction of the dissertation

In this chapter, an introduction was given to the reader on the subject of platinum refining, the potential health risk of soluble platinum salts and the necessity for this study. Furthermore, objectives of the research were identified and hypotheses were stated on the problem statement.

Chapter 2 forms a literature study and includes the following points regarding platinum: literature overview; chemical identification; chemical and physical properties; European Union (EU) classification and labelling; monitoring and analytical methods; occurrence, production and use; occupational exposure; toxicokinetics; biological monitoring, mechanism of toxicity; health effects; existing guidelines, standards, evaluations and recommendations for additional research and a summary.

Chapter 3 includes instructions to authors that want to publish in the *Annals of Occuaptional Hygiene* and the article prefaced by an abstract of the argument and findings, followed by the introduction, methods, results, discussion, and conclusions.

Conclusions and recommendations are made in Chapter 4 regarding the findings of the research and recommendations for future studies.

## 1.3 REFERENCES

1. Acts see South Africa.

2. Baker DB, Gann PH, Brooks SM, Gallagher J, Bernstein IL. (1990) Cross-sectional study of platinum salts sensitization among precious metals refinery workers. Am J Ind Med; 18: 653-664.

3. Bolm-Audorff U, Bienfait HG, Burkhard J, Bury AH, Merget R, Pressel G, Schultze-Werninghaus G. (1992) Prevalence of respiratory allergy in a platinum refinery. Int Arch Occup Environ Health; 64: 257-260.

4. Boshoff JCJ. (2000) A general overview of platinum tailings disposal in South Africa. Mining World: 18, Augustus.

5. Bullock J. (2010) Chloroplatinate Toxicity: Use and Misunderstanding of Merget. International Precious Metals Institute. USA: Tucson, Arizona.

6. Calverley AJ, Murray J. (2005) South Africa's mines: treasure chest or Pandora's box? S Afr J Sci; 101(3): 109-112.

7. Fothergill SJR, Withers DF, Clements FS. (1945) Determination of traces of platinum and palladium in the atmosphere of a platinum refinery. Br J Ind Med; 2: 99-101.

8. Goelzer B. (1996) The 1996 William P. Yant Award Lecture: The Harmonized Development of Occupational Hygiene - a Need in Developing Countries. Am Ind Hyg Assoc J; 57: 984.

9. Health and Safety Executive (HSE) (1996) Platinum metal and soluble platinum compounds in air: laboratory method using electrothermal atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. MDHS46/2. Sudbury (Suffolk), England: HSE Books, ISBN 0 7176 1306 2.

10. Health Council of the Netherlands. (2008) Platinum and platinum compounds. Health-based recommended occupational exposure limit. The Hague: HCN; publication no. 2008/12OSH. ISBN 978 90 5549 718 8.

11. Hunter D, Milton R, Perry KMA. (1945) Asthma caused by the complex salts of platinum. Br J Ind Med; 2: 92-98.

12. Johnson DE, Tillery JB, Prevost RJ. (1975) Levels of platinum, palladium, and lead in populations of southern California. Environ Health Persp; 12: 27-33.

13. Johnson DE, Prevost RJ, Tillery JB, Caman DE, Hosenfeld JM. (1976) Baseline levels of platinum and palladium in human tissue. EPA/600/1-76/019. San Antonio, Texas: Southwest Research Institute. NTIS PB-251 885/0. pp. 252.

14. Merget R, Schultze-Werninghaus G, Muthorst T, Friedrich W, Meier J. (1988) Asthma due to the complex salts of platinum-a cross-sectional survey of workers in a platinum refinery. Clin Allergy; 18: 569-580.

15. Shi ZC. (1987) Platinosis. Proc ICMR Semin 1988 and Proc Asia-Pac Symp. Environ Occup Toxico; 1987: 133-135.

16. South Africa. (1993) Occupational Health and Safety Act (OHSA), No. 85 of 1993. Pretoria: Government Printer.

17. South Africa. (1995) Hazardous Chemical Substances Regulations (HCSR), Regulation 1179 of 25 August, 1995. Pretoria: Government Printer.

18. South Africa. (1996) Mine Health and Safety Act (MHSA), No. 26 of 1996. Pretoria: Government Printer. 2006 Occupational Exposure Limits For Airborne Pollutants.

19. World Health Organization (WHO). (1991) International Programme on Chemical Safety. Geneva, Switzerland: Environmental Health Criteria No. 125.

20. World Health Organization (WHO). (1999) Hazard Prevention and Control in the Work Environment: Airborne Dust. Geneva, Switzerland: WHO/SDE/OEH/99.14. pp. ix-xxiii.

21. World Health Organization (WHO). (2000) Inorganic pollutants: Platinum. In: Air quality guidelines for Europe. Copenhagen. WHO: 166-169.

# CHAPTER 2: LITERATURE OVERVIEW

This chapter reviews existing literature regarding platinum and platinum compounds relevant to this research and includes the following points: literature overview; chemical identification; chemical and physical properties; EU classification and labelling; monitoring and analytical methods; occurrence, production and use; occupational exposure; toxicokinetics; biological monitoring, mechanism of toxicity; health effects; existing guidelines, standards, evaluations and recommendations for additional research.

## 2.1 OVERVIEW

Platinum is a rare but imperative chemical in modern life, used in almost all automotive catalytic converters to reduce pollution, and to catalyse a multitude of energy-efficient industrial processes from petroleum refining to the manufacturing of chemicals, pharmaceuticals and agricultural fertiliser constituents (Bullock, 2010). The production of platinum, and of platinum catalysts, involves the formation of chloroplatinates, because platinum does not dissolve outside of chlorine-based chemistry. While platinum itself (platinum metal) is considered to be non-toxic, chloroplatinates are potent skin and respiratory sensitisers, and PSS is a long-known and significant health problem in the platinum industry. Even in modern, well-controlled working environments, about 1% of (40 out of 4000) workers exposed to chloroplatinates are sensitised annually (Bullock, 2010). Once sensitised, the concentration that elicits an adverse response is lower and complete removal of the sensitised worker from the platinum industry where chloroplatinates are present may be necessary. The exact exposure conditions that cause sensitisation, however, are not yet known. Symptoms of sensitisation do not appear immediately, and a subsequent chloroplatinate exposure that elicits a response may occur much later, making it more difficult to find the conditions of the original sensitisation. Direct contact and dermal exposure to chloroplatinates, or minute, sharp exposures above the standard level could contribute to the sensitisation observed (Lindell, 1997; WHO, 2000; Health Council of the Netherlands, 2008). An 8-hour TWA exposure limit of 2 $\mu g/m^3$ for water-soluble species of platinum is imposed in most countries with platinum industry activity. Even so, there can and has been sensitisation at levels well below this limit and this led to the question, is this limit completely protective? A science-based threshold of exposure that causes sensitisation has not yet been found. This is a matter of increasing concern and improved control measures such as substitution of non-sensitising platinum species, enclosed and automated processing, optimal ventilation, occupational hygiene monitoring, etc., together with close medical surveillance need to be implemented in the platinum industry (Lindell, 1997; Health Council of the Netherlands, 2008; Bullock, 2010).

## 2.2 CHEMICAL IDENTIFICATION

The most relevant platinum compounds are listed in Table 1.

Table 1. Chemical identification of platinum and relevant platinum salts (Lide, 1995).

| Chemical name synonyms | Formula | Molecular weight | CAS number | EINECS number | EEC number | RTECS number |
|---|---|---|---|---|---|---|
| Platinum<br>platin, platinum metal, platinum black, platinum sponge, liquid bright platinum | Pt | 195.09 | 7440-06-4 | 231-116-1 | not listed | TP2160000 |
| Platinum oxide<br>platinum monoxide, platinum(II) oxide, platinous oxide | PtO | 211.08 | 12035-82-4 | 234-831-7 | not listed | not listed |
| Platinum dioxide<br>platinum(IV) oxide, platinic oxide | $PtO_2$ | 227.08 | 1314-15-4 | 215-233-0 | not listed | not listed |
| Platinum monosulfide<br>platinum(II) sulphide | PtS | 227.15 | 12038-20-9 | 234-875-7 | not listed | not listed |
| Platinum disulfide<br>platinum(IV) sulphide | $PtS_2$ | 259.21 | 12038-21-0 | 234-876-2 | not listed | not listed |
| Platinum dichloride<br>platinum(II) chloride, platinous (di)chloride | $PtCl_2$ | 265.99 | 10025-65-7 | 233-034-1 | not listed | TP2275000 |
| Platinum tetrachloride,<br>platinum(IV) chloride,<br>tetrachloroplatinum | $PtCl_4$ | 336.89 | 13454-96-1 | 236-645-1 | not listed | TP2275550 |
| Platinum sulfate (tetrahydrate) | $Pt(SO_4)_2.4H_2O$ | 459.27 | - | not listed | not listed | not listed |
| Hexachloroplatinic acid<br>(chloro)platinic acid,(di)hydrogen hexachloroplatinate | $H_2PtCl_6$ | 409.81 | 16941-12-1 | 241-010-7 | 078-009-00-4 | TP1500000 |
| Diammonium tetrachloroplatinate<br>ammonium tetrachloroplatinate(II), ammonium chloroplatinite, platinous ammonium chloride | $(NH_4)_2PtCl_4$ | 372.97 | 13820-41-2 | 237-499-1 | 078-002-00-6 | TP1840000 |
| Diammonium hexachloroplatinate<br>ammonium hexachloroplatinate(IV), platinic ammonium chloride | $(NH_4)_2PtCl_6$ | 443.87 | 16919-58-7 | 240-973-0 | 078-008-00-9 | BP5425000 |
| Dipotassium tetrachloroplatinate<br>potassium tetrachloroplatinate(II), potassium chloroplatinite, platinous potassium chloride | $K_2PtCl_4$ | 415.09 | 10025-99-7 | 233-050-9 | 078-004-00-7 | TP1850000 |
| Dipotassium hexachloroplatinate<br>potassium hexachloroplatinate(IV), platinic potassium chloride | $K_2PtCl_6$ | 485.99 | 16921-30-5 | 240-979-3 | 078-007-00-3 | TP1650000 |
| Disodium hexachloroplatinate<br>sodium hexachloroplatinate(IV), sodium platinum chloride | $Na_2PtCl_6$ | 453.77 | 16923-58-3 | 240-983-5 | 078-006-00-8 | not listed |
| Tetraammineplatinum dichloride<br>platinumtetraammine dichloride, tetraamminedichloroplatinum(II) tetraammineplatinum(II) chloride | $[Pt(NH_3)_4]Cl_2$ | 334.11 | 13933-32-9 | not listed | not listed | not listed |

CAS, Chemical Abstracts Service; EINECS, European Inventory of Existing Chemical Substances; EEC, European Commission; RTECS, Registry of Toxic Effects of Chemical Substances.

## 2.3 PHYSICAL AND CHEMICAL PROPERTIES

Platinum (Pt) is a malleable, ductile, silver-grey noble metal with the atomic number 78 and an atomic weight of 195.09. It belongs to group 10 of the periodic system, and has six naturally occurring isotopes: $^{190}Pt$, $^{192}Pt$, $^{194}Pt$, $^{195}Pt$, $^{196}Pt$, and $^{198}Pt$. The most abundant of these is $^{195}Pt$, comprising 33.83% of all platinum. The maximum oxidation state for platinum is +6 (platinum hexafluoride), with the oxidation states of +2 and +4 being the most stable. Platinum is relatively inert and does not react readily with oxygen or many acids (Mastromatteo, 1983; IPCS, 1991; WHO, 2000; Health Council of the Netherlands, 2008).

### 2.3.1 Platinum metal

The metal does not corrode in air at any temperature, but can be affected by halogens, cyanides, sulphur, molten sulphur compounds, heavy metals, and hydroxides (Lindell. 1997; WHO, 2000; Health Council of the Netherlands, 2008). Digestion of platinum metal with aqua regia or concentrated hydrochloric acid, through which chlorine gas is bubbled ($Cl_2$/HCl) produces hexachloroplatinic acid an important platinum complex (IPCS, 1991).

### 2.3.2 Platinum compounds

The chemistry of platinum compounds in aqueous solution is dominated by the complex compounds. Many of the salts, particularly those with halogen or nitrogen-donor ligands, are water-soluble. Platinum, like the other platinum group metals (PGMs), has a marked tendency to react with carbon compounds, especially alkenes and alkynes, forming platinum(II) coordination complexes (IPCS, 1991; Lindell, 1997; Health Council of the Netherlands, 2008).

### 2.3.3 Platinum solubility

The solubility in water also differs between platinum compounds. Platinum metal and platinum oxides are insoluble, while complex hexachloroplatinate salts sparingly dissolve in water. The tetrachloroplatinates are more easily soluble than the corresponding hexachloroplatinates (Lindell, 1997). Some physical and chemical constants of platinum compounds are given in Table 2 (Health Council of the Netherlands, 2008).

Table 2. Physical and chemical properties of platinum compounds and its relevant platinum salts (Lide, 1995; Health Council of the Netherlands, 2008).

| Chemical name | Formula | Molecular weight | Melting point (°C) | Density (kg/m$^3$) | Solubility in water |
|---|---|---|---|---|---|
| Platinum [a] | Pt | 195.09 | 1768 | 21.45 [b] | Insoluble |
| Platinum oxide | PtO | 211.08 | 325 [c] | 14.1 | Insoluble |
| Platinum dioxide | $PtO_2$ | 227.08 | 450 | 11.8 | Insoluble |
| Platinum monosulfide | PtS | 227.15 | - | 10.25 | Insoluble |
| Platinum disulfide | $PtS_2$ | 259.21 | 225 ï 250 [c] | 7.85 | Insoluble |
| Platinum dichloride | $PtCl_2$ | 265.99 | 581 [c] | 6.0 | Insoluble |
| Platinum tetrachloride | $PtCl_4$ | 336.89 | 327 [c] | 4.30 | slightly soluble |
| | | | - [d] | 2.43 [d] | Soluble [d] |
| Platinum sulfate | $Pt(SO_4)_2.4H_2O$ | 409.27 | - | - | Soluble |
| Hexachloroplatinic acid | $H_2PtCl_6$ | 459.81 | 60[e] | 2.43 [e] | very soluble [e] |
| Diammonium tetrachloroplatinate | $(NH_4)_2PtCl_4$ | 372.97 | - [c] | 2.94 | Soluble |
| Diammonium hexachloroplatinate | $(NH_4)_2PtCl_6$ | 443.87 | 380 [c] | 3.07 | slightly soluble |
| Dipotassium tetrachloroplatinate | $K_2PtCl_4$ | 415.09 | 500 [c] | 3.38 | Soluble |
| Dipotassium hexachloroplatinate | $K_2PtCl_6$ | 485.99 | 250 [c] | 3.50 | slightly soluble |
| Disodium hexachloroplatinate | $Na_2PtCl_6$ | 453.77 | 250 [c] | 3.50 | very soluble [e] |
| Tetraammineplatinum dichloride | $[Pt(NH_3)_4]Cl_2$ | 333.98 | 250 [c] | 2.70 | Soluble |

a, the boiling point of Pt is 3825°C; b, at 20°C; c, decomposes; d, pentahydrate; e, hexahydrate; f monohydrate.

## 2.4 EU CLASSIFICATION AND LABELLING

Platinum itself and some platinum salts have not been classified and labelled (see Table 1), however, the platinum salts which have been classified and labelled by the EU are listed in Table 3.

Table 3. EU classification and labelling of relevant platinum salts (Health Council of the Netherlands, 2008).

| Substance | EINECS number | Classification and risk phrases | Safety phrases |
|---|---|---|---|
| Hexachloroplatinic acid $H_2PtCl_6$ | 241-010-7 | T, R25; C, R34; R42/43 | 1/2 ï 22 ï 26 ï 36/37/39 ï 45 |
| Diammonium tetrachloroplatinate $(NH_4)_2PtCl_4$ | 237-499-1 | T, R25; Xi, R38-41; R42/43 | 2 ï 22 ï 26 ï 36/37/39 ï 45 |
| Diammonium hexachloroplatinate $(NH_4)_2PtCl_6$ | 240-973-0 | T, R25; Xi, R41; R42/43 | 1/2 ï 22 ï 26 ï 36/37/39 ï 45 |
| Dipotassium tetrachloroplatinate $K_2PtCl_4$ | 240-973-0 | T, R25; Xi, R38-41; R42/43 | 2 ï 22 ï 26 ï 36/37/39 ï 45 |
| Dipotassium hexachloroplatinate $K_2PtCl_6$ | 240-979-3 | T, R25; Xi, R41; R42/43 | 1/2 ï 22 ï 26 ï 36/37/39 ï 45 |
| Disodium hexachloroplatinate $Na_2PtCl_6$ | 240-983-5 | T, R25; Xi, R41; R42/43 | 1/2 ï 22 ï 26 ï 36/37/39 ï 45 |

T, Toxic; Xi, Irritant; C, Corrosive; R25, Toxic if swallowed; R34, Causes burns; R38, Irritating to skin; R41, Risk of serious damage to eyes; R42/43, May cause sensitisation by inhalation and skin contact; S1/2, Keep locked up and out of the reach of children; S2, Keep out of the reach of children; S22, Do not breathe dust; S26, In case of contact with eyes, rinse immediately with plenty of water and seek medical advice; S36/37/39, Wear suitable protective clothing, gloves and eye/face protection; S45, In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

## 2.5 MONITORING AND ANALYTICAL METHODS

Several organisations, such as the UK Health and Safety Executive (HSE) (method MDHS 46) (HSE, 1996), United States National Institute for Occupational Safety and Health (NIOSH) (method 7300 and 7303) (NIOSH, 1994, 2003) and the Occupational Safety and Health Administration (OSHA) (method ID121 and method ID130SG) (OSHA 1985, 1991), have described methods that can be used for analysing platinum and platinum compounds in workplace air (Lindell, 1997; Health Council of the Netherlands, 2008).

A measured volume of air is filtered through a specified filter depending on the method used. Loaded filters are treated with acid solutions, and the extracts are analysed by specific spectrometric techniques. Generally, lengthy sampling periods are necessary. The methods cannot distinguish between platinum and platinum compounds. Although several techniques were described by NIOSH for the analysis of platinum in biological samples, there were no external quality assessment schemes for these analyses available, and for that reason not validated (Lindell, 1997; Health Council of the Netherlands, 2008).

### 2.5.1 Air monitoring

The HSE method, MDSH 46 (HSE, 1985), has been reviewed and replaced. The principal changes in method MDSH 46/2 (date: December 1996) are to recommend the use of filters that are soluble using the dissolution technique described for platinum metal, and to describe the use of inductively coupled plasma mass spectrometry (ICP-MS) for the analysis of sample solutions with a low platinum concentration (HSE, 1996). The method is suitable for the determination of platinum metal and soluble platinum compounds in workplace air. The majority of insoluble platinum compounds in industrial use or occurring in workplace air is also determined by the method for platinum metal. The method does not distinguish between halogeno-platinates and other soluble platinum compounds (Health Council of the Netherlands, 2008).

A known volume of air is drawn through a filter mounted in an inhalable dust sampler. If soluble platinum compounds are to be determined, the filter and collected sample are treated with 5 mL of 0.07 M hydrochloric acid and agitated by mechanical shaking or using an ultrasonic bath. The leach solution is then filtered under suction through a mixed cellulose ester (MCE) membrane filter of 0.8 μm mean pore diameter and diluted to 10 mL. The resultant solution is analysed by either electrothermal atomic absorption spectrometry (AAS) or ICP-MS. If platinum metal is also to be determined, the secondary filter used for filtration of the leach solution is kept for further treatment (HSE, 1996).

The method for soluble compounds has shown to be suitable for use with sampling times in the range 30 minutes to 8 hours for analysis by IPC-MS, and for sampling times in the range 4-8 hours for analysis by electrothermal AAS. The method for metal is suitable for use with sampling times in the range 30 minutes to 8 hours using either analytical technique. The qualitative and quantitative detection limits for platinum, defined as 3 fold and 10 fold the standard deviation of a blank determination, have been determined to be 3.6 ng/L and 12 ng/L for electrothermal AAS, and 0.003 ng/L and 0.010 ng/L for IPC-MS. For an air sample volume of 30 L and a sample solution volume of 10 mL, this corresponds to platinum in air concentrations of 1 $\mu g/m^3$ and 4 $\mu g/m^3$ for electrothermal AAS, and 1 $pg/m^3$ and 3 $pg/m^3$ for IPC-MS. The method is validated to demonstrate compliance with the general requirements described by the Comité Européen de Normalization (CEN) (in European Standard EN 482) (CEN, 1995; HSE, 1996)

NIOSH has published another method for the determination of elements, including platinum, in air, method 7303 (date: March 2003). This method is similar to NIOSH method 7301 differing only in the use of the hot block for digestion of the sampler. Sample solutions are analysed by inductively coupled plasma-atomic emission spectrometry (ICP-AES) (NIOSH, 2003). Alternative, more sensitive methods exist for some elements by graphite furnace atomic absorption spectroscopy (GFAAS).

OSHA has described a specific method for the determination of platinum in workplace atmospheres (method ID130SG; date: March 1985) (OSHA, 1985). Air that contains particles is collected on 0.8 μm MCE membrane filters, with a sampling rate of 2 L/min; the recommended air volume is in the range between 250-960 L and the sampling time should be at least 7 hours. Loaded filters are extracted with deionised water and the filtrate is subsequently acidified with nitric acid. Sample solutions are analysed using GFAAS with detection limits reported to be 0.01 μg/mL (OSHA, 1985).

Flame atomic absorption or emission spectrometry used in the OSHA method ID121 (OSHA, 1991) showed a poor detection limit for platinum when compared to GFAAS. However, GFAAS might not be suitable for short term exposures when the platinum concentration is low. Sample solutions may then be analysed by ICP-MS, which exhibits a significantly lower detection limit for platinum compared to GFAAS.

## 2.6 OCCURRENCE

### 2.6.1 Natural occurrence

Platinum, together with the other PGMs (palladium, rhodium, ruthenium, iridium, and osmium) are concentrated mainly in the iron-nickel core during the earth's formation. This explains their relatively low presence in the lithosphere (rocky crust) where the average concentration of platinum ranges between 0.001-0.005 mg/kg, composing about 5 x $10^{-7}$% of the earth's crust (Renner and Schumuckler, 1991; Greenwood and Earnshaw, 1997; Health Council of the Netherlands, 2008). Platinum is found both in its metallic form and in a number of minerals. In its natural state, platinum generally is alloyed with small amounts of the other platinum metals or with iron and occurs as a blend of fine grains or nuggets in alluvial deposits in Russia, Alaska and Columbia. The economically significant sources of platinum metal are in Russia, South Africa and Canada, where it can be found in small quantities in nickel and copper ores (Lindell, 1997; Health Council of the Netherlands, 2008). The platinum content in deposits derived from Russia and South Africa is between 1-500 mg/kg and 0.3 mg/kg for deposits from Canada.

The principal minerals containing platinum are sperrylite ($PtAs_2$), cooperite ([Pt,Pd]S) and braggite ([Pt,Pd,Ni]S) (IPCS, 1991). Primary deposits are associated with ultrabasic, rather than silicic, rock formations (Mastsromatteo, 1983). Small amounts of platinum are also mined from secondary or placer deposits in the Ural Mountains, Colombia, Alaska, Ethiopia, and the Philippines. In these deposits platinum is present in the form of metallic alloys of varied composition (IPCS, 1991).

### 2.6.2 Occurrence in air

The occurrence of platinum in ambient air before the introduction of vehicles with catalytic converters was mainly dependent on the concentration in nature, that is, in soil and fertilisers (Lindell, 1997; Health Council of the Netherlands, 2008). Mean concentration of platinum in 1973 near a highway outside the city of Ghent (Belgium) was reported (Schutyser *et al.*, 1977) to be less than 10 pg/m$^3$. Air samples taken near a freeway in California in 1974, when few car catalysts were used, were below the detection limit of 0.05 pg/m$^3$ (Johnson *et al.*, 1975). In Germany, platinum air concentrations measured close to city roads in 1989 were at most 13 pg/m$^3$ but in rural areas the concentrations were much smaller (1.8 pg/m$^3$). At that time few German cars were equipped with catalysts and these levels could reflect background levels (IPCS, 1991; WHO, 2000).

In 1984 and 1991 platinum concentrations in road dust were measured in Sweden and a significant increase in platinum concentrations was observed from 1984 to 1991 (Wei and Morrison, 1994). In a more recent study platinum air levels between 0.3-30 pg/m$^3$ were measured in Germany (Alt and Messerschmidt, 1993; cited in the Health Council of the Netherlands, 2008).

Platinum concentrations in ambient air reported from 1995 onward for European cities (Frankfurt am Main, Göteborg, Madrid, Munich and Rome) are essentially similar to the concentrations mentioned above. Platinum airborne dust samples taken in downtown areas varied between 7-23 pg/m$^3$ and for the ring roads of these cities the values were between 4-18 pg/m$^3$ (Rosner and Merget, 2000; Gomez *et al.*, 2002; Zereini *et al.*, 2004). The tracheo-bronchial fraction (3.14-10.2 μm) represented approximately 21% and the alveolar fraction (<3.14 μm) approximately 14% (Gomez *et al.*, 2002).

Platinum emissions from automotive catalytic converters using different operating conditions (four converters; new and aged converters; constant speed simulations and standard driving cycles; a 1.8 L and a 1.4 L engine) were studied by Artelt *et al.* (1999a). Depending on these conditions or a combination of these conditions, the mean platinum emissions ranged from 7-123 ng/m$^3$ corresponding to emission factors between 9-124 ng/km. Platinum was almost exclusively bound to aluminium oxide particles of which 43-74% had an aerodynamic diameter >10 μm; the alveolar fraction (<3 μm) ranged from 11-36%. Only a very small quantity (<1%) of the total platinum emitted may consist of soluble platinum compounds (Artelt *et al.*, 1999a).

Catalytic converters have been identified as mobile sources of platinum since small quantities of platinum are emitted resulting from mechanical and thermal impact. The pellet-type, introduced initially in the United States but never used in Europe, was estimated to emit up to approximately 2 μg of platinum for every kilometre travelled. Of the particles emitted, 80% had diameters greater than 125 μm (WHO, 2000). The proportion of the respirable fraction is not known.

Emission of platinum from the new generation three-way monolith-type catalytic converter, currently used in the United States and Europe, is lower by a factor of 100 to 1000 when compared with the earlier type (IPCS, 1991). Platinum emission from the generally used monolith-type catalysts used in Europe has been calculated to be 2 ng/km (at 60 km/h) to 40 ng/km (at 140 km/h) (König *et al.*, 1992). Platinum emissions were observed to increase with speed and with increasing exhaust gas temperature.

Based on dispersion models used by the United States Environmental Protection Agency (EPA) and assuming an average emission rate of approximately 20 ng/km, the ambient air concentrations of total platinum near or on roads were calculated to be up to 0.09 ng/m$^3$ (the highest values recorded are in a roadway tunnel) (IPCS, 1991; König *et al.*, 1992). The chemical nature of the platinum emissions has not been fully determined, but in the case of the first-generation pellet-type catalyst used in the United States only 10% of the platinum emitted was water-soluble (Rosner and Merget, 1990). Metallic platinum reacted with oxygen to form platinum(IV) oxide at temperatures above 500°C (as in the exhaust converter).

According to an assessment made by the international programme on chemical safety (IPCS), it is not possible to conclude if micro-organisms in the environment are able to biomethylate platinum compounds (IPCS, 1991).

### 2.6.3 Occurrence in food

Hamilton and Minski (1972/1973) (cited in IPCS, 1991) estimated a total daily platinum intake of less than 1 µg/day, based on an analysis of a United Kingdom total-diet sample and 1963 United Kingdom consumption and population figures. It must be noted that no data were given on the platinum content of the foods analysed.

In 1986 a study of platinum levels in a range of foodstuffs from Sydney, Australia was conducted by Vaughan and Florence (1992). Foods were prepared using normal cooking procedures, then either blended and air-dried or lyophilised, analysis being carried out by adsorptive voltammetry (AV). The platinum levels ranged between 8.11 µg/kg (liver) and 0.13 µg/kg (full-cream milk). Platinum concentrations were highest in eggs and offal, with a mean concentration of 5.8 µg/kg, followed, in decreasing order, by meat (mean 3.2 µg/kg), grain products (mean 3.2 µg/kg), fish (mean1.8 µg/kg), fruit and vegetables (mean 0.82 µg/kg) and dairy products (mean 0.27 µg/kg). Using hypothetical diets compiled by the Australian Federal Department of Health, the daily platinum intake for adults from the diet was calculated to be 1.44 µg. When food samples were analysed from Lord Howe Island in the South Pacific, an island with few cars and little pollution; similar platinum levels were found (Lindell, 1997; WHO, 2000).

The Total Diet Study, an important part of the United Kingdom Governmentôs surveillance programme for chemicals in food, estimated that the mean total dietary platinum exposure for adults was up to 0.2 µg/day (upper range: 0.3 µg/day). This surveillance programme did not include the contribution from drinking water. This figure was estimated from the mean concentrations of platinum (limit of detection: 0.1 µg/kg fresh weight) in 20 food groups and the average consumption of each food group from a national food survey (Ysart *et al.*, 1999).

The dietary intake of 84 young German children (age: 14-83 months) was in the range of <0.01-450 ng/kg dry weight (dw)(median: 22 ng/kg), corresponding with <0.81-32 ng/kg body weight per week (bw/w) (median: 2.3 ng/kg). Wittsiepe *et al.* (2003) reported that children consuming exclusively products from the supermarket showed slightly higher platinum concentrations in the food and a higher dietary intake per bw than children eating vegetables and domestic animals from their own gardens and/or surrounding areas.

### 2.6.4 Occurrence in water and sediments

In highly industrialised areas anthropogenic sources of platinum have given rise to elevated levels in river sediments. Dissanayake *et al*. (1984) reported a very high level of pollution in sediments of the river Rhine, Germany, with values ranging from 734-31 220 µg/kg dw. These values differ significantly (higher by a factor of up to 15 000) when compared to the values of unpolluted North Sea sediments. The extremely high concentrations appeared at the interface between an extremely reducing and an oxidizing aquatic environment that provided, together with a pH of 6.6-7.8, optimum conditions for the formation of metal-organic complexes. The sample containing 31 220 µg Pt/kg also contained the highest concentration of palladium (4000 µg/kg). The gold content (100-400 µg/kg) had a relatively uniform distribution, but also indicated a high state of pollution (IPCS, 1991).

Platinum levels in drinking-water have been estimated at 0.0001 µg/L, with similar values recorded for glacier ice (WHO, 2000). However, Van den Berg and Jacinto (1988) reported very high levels of platinum in tap-water from Liverpool, at 0.06 µg/L, but further investigations are necessary. The same investigators (Van den Berg and Jacinto, 1988) reported platinum levels ranging from 0.000037-0.000154 µg/L for shallow and deep-sea water samples respectively, whereas coastal sea water contained 0.000332 µg/L. It should be noted that these were only single samples (IPCS, 1991).

Goldberg *et al*. (1986) reported platinum levels between 0.0001-0.0002 µg/L for samples taken from the Pacific Ocean and 0.0022 µg/L for samples taken from the Baltic Sea. In filtered samples from the Pacific, platinum levels have been shown to increase with depth, showing nutrient-like profiles from surface values of 0.0001-0.00025 µg/L at 4500 m (Goldberg and Koide, 1990).

## 2.7 PRODUCTION

Platinum is obtained from large-scale underground ore mining and recycled metal (Hughes, 1980). The ore is concentrated following flotation and smelting operations, and individual metals are separated and refined by complex chemical treatments that require sophisticated chemical technology. During the refining the concentrate is dissolved in aqua regia (nitro-hydrochloric acid) or concentrated hydrochloric acid through which chlorine gas is bubbled ($Cl_2$/HCl). Hexachloroplatinic(IV) acid or sodium hexachloroplatinate(IV) is formed and in both cases addition of ammonium chloride leads to the formation of ammonium hexachloroplatinate(IV), a yellow salt (Hughes, 1980; IPCS, 1991).

After several purification processes there is a second precipitation of this complex salt, which is then filtered off, dried and calcined at 600-700°C to yield a crude platinum metal sponge, which undergoes further refining. Finally, after heating up to 1000°C a grey metal sponge of platinum >99.9% pure is produced (Hughes, 1980). There are other methods of purification: e.g. platinum can be reduced to the metal from aqueous solution of its salts, whereby a black powder of platinum metal (platinum black) is produced (Mastromatteo, 1983; IPCS, 1990; Beliles, 1994). Hexachloroplatinic(IV) acid, the most important platinum compound (formed when platinum is dissolved in aqua regia), is isolated as the hydrate and is the source of many other platinum compounds (Beliles, 1994).

The world production of platinum group metals (40ï 50% of which is platinum) has increased steadily over the past two decades, with a total of 127 tonnes in 1971 rising to 270 tonnes (with108ï 135 tonnes of platinum) in 1987 *(*Loebenstein, 1988) and 152 tonnes in 1995 (WHO 2000). In 2005, the world supply of platinum amounted to 225 tonnes, an increase of roughly 50% compared with the period 1995-2000. Most of this supply originated from mine production (78%), the remainder from Russian exports (10%) and secondary sources (10%) such as scrap (recovery from auto catalysts). South Africa is by far the major mine producer accounting for 90%, followed by Canada (4%), Zimbabwe (3%), and the USA (2%). Demands are expected to increase further due to the increasing demand for autocatalysts and the anticipated further development of fuel cells. (Health Council of the Netherlands, 2008).

## 2.8 USE

Platinum has exceptional catalytic properties and is used in the chemical and petroleum industries in hydrogenation, isomerisation, cyclisation, dehydration, dehalogenation and oxidation reactions (Mastromatteo, 1983; Beliles, 1994). Major uses are in ammonia oxidation, in the production of nitric acid and in the catalytic upgrading of the octane rating of gasoline. Platinum and some inorganic platinum compounds are used in Sweden for naphtha-reforming to upgrade the octane rating of gasoline and during the production of organic base chemicals e.g. for cleaning of gases (Health Council of the Netherlands, 2008). In the past few years platinum and its salts are mainly used in the automotive industry (as catalysts in automobile exhausts). A motor vehicle catalytic converter contains 1-3 g of platinum. Catalytic converters were introduced in 1975 in the United States to meet the stringent emission limits of the Federal Clean Air Act, and became mandatory in the European Community in 1993. Platinum-rhodium or platinum-palladium catalysts are used to control emissions from automobile exhausts and oxidize carbon monoxide and unburnt hydrocarbons and in the case of platinum-rhodium, nitrogen oxides are reduced (Bradford, 1988; IPCS, 1991).

In Finland at least four products containing platinum are used as catalysts or laboratory chemicals. Few data on the chemical composition or the amounts used have been obtained, but it has been stated that 300 kg/year of platinum (tetraammineplatinum hydrogencarbonate) is used by a producer of automobile catalysers (personal communication, V. Riihimäki, Finnish Institute of Occupational Health; cited in Lindell, 1997).

Resistance to many forms of corrosion and strength at high temperatures are other significant properties of platinum and it is often alloyed with other platinum or base metals used in electric contacts for relays, printed circuits (in the electronics industry), laboratory and plant apparatus, electrochemical anodes, spinnerets used for synthetic fibre extrusion, bushings for the production of fibreglass and vessels used for example in glass-making industry. Platinum is also used to produce a silvery lustre on ceramic glazes (Mastromatteo, 1983; Bradford, 1988; IPCS, 1991; Beliles, 1994). Some alloys containing platinum are used in dentistry and medicine and include dental and neurological prostheses, for recording electrical activity, and for pacemaker electrodes. Potassium tetrachloroplatinate(II) possibly may be used as a dental drug (dentine desensitiser) (Kanematsu *et al.*, 1990). Certain platinum complexes, like cisplatin and its analogues are used as anticancer drugs for the treatment of testicular and metastatic ovarian tumours and in lung and bladder cancer (Lindell, 1997; Health Council of the Netherlands, 2008).

Platinum salts may be used e.g. in the manufacture of platinum catalysts, for electroplating, and for photographic applications. Hexachloroplatinic(IV) acid may be used in platinising alumina or charcoal in catalyst production (IPCS, 1991). A number of salts can be used in the electrode-position of platinum. Industrial items e.g. aviation components, electrodes, turbine blades and wire, as well as jewellery and decorative items may be electroplated with platinum. Potassium tetrachloroplatinate(II) (used as a toner in the developing of photographic paper) and potassium hexachloroplatinate(IV), are soluble platinum salts used in the photographic industry (Mastromatteo, 1983; Woolf and Ebert, 1991). In 2005, 62 tonnes of platinum were used in Europe, of which about 76% was used in the automotive industry (catalysts). Germany, United Kingdom, and France used about 4% in jewellery and 2% in electronics, and Germany used about 2% in dentistry. Worldwide, 51% of the amount produced was used in the automotive industry, 12% in jewellery, 4% in electronics, and 4% in chemical/petroleum refining with smaller amounts (1%) used in dentistry and medicine (as anti-cancer drugs such as cisplatin and carboplatin) (Lindell, 1997; Health Council of the Netherlands, 2008).

Before the introduction of automobile catalytic converters most of the platinum was used as catalysts in the chemical and petroleum industry. Platinum sales are reported in Table 4 for the different United States industries before and after the introduction of automobile catalytic converters.

Table 4. Platinum sales to various types of industry in the United States before and after the introduction of automobile catalytic converters (IPCS, 1991).

| Industry | kg/year (1973) | % of total (1973) | kg/year (1987) | % of total (1987) |
|---|---|---|---|---|
| Automobile | - | - | 18817 | 71.3 |
| Chemical | 7434 | 36.3 | 1920 | 7.5 |
| Petroleum | 3844 | 18.8 | 739 | 2.8 |
| Dental and medical | 868 | 4.2 | 479 | 1.9 |
| Electrical | 3642 | 17.9 | 1821 | 7.1 |
| Glass | 2255 | 11.0 | 285 | 1.1 |
| Jewellery and decorative | 697 | 3.4 | 177 | 0.7 |
| Miscellaneous | 1732 | 8.5 | 1430 | 5.6 |
| Total | 20472 | 100 | 25668 | 100 |

## 2.9 OCCUPATIONAL EXPOSURE

Occupational exposed workers demonstrated the highest levels of platinum exposure via inhalation (WHO, 2000). Many countries have set OELs. In the United States, the threshold limit value time-weighted average (TLV-TWA) for daily occupational exposure has been established for soluble platinum salts at 0.002 mg/m$^3$ and at 1 mg/m$^3$ for platinum metal (ACGIH, 1990). In the United Kingdom, an 8-hour TWA OEL of 0.002 mg/m$^3$ has been proposed for soluble platinum salts and a limit of 5 mg/m$^3$ for platinum metal (as total inhalable dust) (HSE, 1990, 1996). In the Republic of South Africa both the Department of Labour and the Department of Minerals and Energy issue OELs for airborne pollutants. The OELs from the Department of Labour are based on the OELs of the United Kingdom and described in the Hazardous Chemical Substances Regulations (Annexure 1) of 1995 (HCSR, 1995). The OELs from the Department of Minerals and Energy are described in the Occupational Hygiene Regulations of 2006, OELs for Airborne Pollutants Schedule 22.9(2)(a) (MHSA, 1996).

Mining, refining and processing are the three primary industrial sources that contribute to occupational exposure of platinum. In the mining operation platinum is usually found in the insoluble form, as the free metal or in very insoluble forms (Health Council of the Netherlands, 2008). Soluble forms of platinum are mainly produced in the refining operations, especially during the final steps. Occupational exposure to chloroplatinic acid or complex halogenated salts of platinum (e.g. ammonium and sodium hexa- and tetrachloroplatinate) is considered to occur in the primary refining of platinum and during secondary refining (when platinum is reclaimed from scrap metal and expended catalysts (Baker ***et al.***, 1990; Bernstein and Brooks, 1993).

Occupational exposure to hexachloroplatinic(IV) acid or platinum salts might also be anticipated in the manufacture of automobile emission control systems, catalysts for agricultural fertilisers, at small-scale plating or coating operations, during laboratory handling and in the photographic industry (Mastromatteo, 1983; Baumgärtner and Raub, 1988; Skinner, 1989; Woolf and Ebert, 1991; HSE, 1996). Exposure to certain platinum compounds e.g. antineoplastic drugs also might occur in hospitals (Ensslin *et al.*, 1994). Table 5 includes some available information regarding platinum levels in different work environments, but the exposure data may not be directly comparable due to inconsistent sampling and analytical techniques.

Table 5. Workplace concentrations of platinum in various types of industries (Health Council of the Netherlands, 2008).

| Industry | Process, work operation | Concentration μg/m$^3$ | Country | Study |
|---|---|---|---|---|
| Mine | mine, furnace room<br>precious metals area | <0.003<br>0.377 | Sudbury (Canada) | Johnson *et al.*, 1976 |
| | refining of platinum-iridium alloy | 5000-80000 | China | Shi, 1987 |
| Platinum refinery | crushing $(NH_4)_2(PtCl_6)$ | <1700 | United Kingdom | Fothergill *et al.*, 1945 |
| | discharging $(NH_4)_2(PtCl_6)$ fr ovens | >68 | | Hunter *et al.*, 1945 |
| | sieving platinum metal | 400-960 | | |
| | neutralizing platinum salts | 18-20 | | |
| | other areas | 0.9-9.5 | | |
| Platinum refinery | salts section<br>refinery section | 0.13-0.21<br>0.02-0.26 | New Jersey | Johnson *et al.*, 1976 |
| Platinum refinery | generally | <0.08 | Germany | Merget *et al.*, 1988 |
| Platinum refinery | separation shop<br>generally | 0.08, 0.1<br><2.0 | Germany | Bolm-Audorff *et al.*, 1992 |
| Platinum refinery | refining, catalyst manufacture<br>handling and dispensing of solids and solutions | <2<br><16 | United Kingdom | HSE, 1996 |
| Platinum refinery | refining | 0.01 to 26 (15 min)<br>0.06 to 13.6 (6-8h) | United Kingdom | Maynard *et al.*, 1997 |
| Platinum catalyst manufacturing | catalyst manufacture | 0.02 to 10.82 (15 min)<br>0.03 to 0.6 (6-8h) | United Kingdom | Maynard *et al.*, 1997 |
| Manufacture metal-coated electrodes | generally | 0.03 and 0.99 (15 min)<br>0.003 to 0.079 (6-8h) | United Kingdom | Maynard *et al.*, 1997 |
| Platinum recycling industry | recovery<br>refinery<br>warehouse<br>analytical laboratories<br>other areas | 2.7, 5.3<br>10.7, 27.1<br>8.6<br>0.4<br>0.5, 0.6 | United States of America | Baker *et al.*, 1990 |
| Platinum recycling industry | cutting<br>cutting<br>draining<br>draining<br>generally | 15<br>10 (in resp. dust)<br>71<br>24 (in resp. dust)<br><1 | Sweden | Gerd Sällsten, department of Occupational Medicine, Gothenburg, Sweden, personal communication 1996 |
| Precious catalysts reprocessing plant | destruction of spent catalysts | 40 - 240 | France | Hery *et al.*, 1994 |
| Platinum metal using industry | production of catalysts<br>grinding, polishing, cutting, sawing<br>recycling of platinum catalysts | 0.3-19.9<br>1.8-3.1<br>3.8 | | Schaller *et al.*, 1992 |
| Platinum metal using industry | production of catalysts | 0.005 to 0.7 (area)<br>0.05 to 3.7(personal) | Germany | Merget, 2000; Merget *et al.*, 2000; Merget and Rosner, 2001 |
| Car catalyst manufacturing | dilution of hexachloroplatinic acid, coating of catalysts, packing area, lab work | <0.4 | Sweden | Granlund, 1991 (Cited in Health Council of the Netherlands, 2008) |
| Manufacture of platinum-coated oxygen sensors | generally | 0.14-1.83 | Japan | HSE, 1996<br>Shima *et al.*, 1984 |
| Production, recovery, and recycling of catalytic converters | coating department | 1.21 (area-mean)<br>2.70 (personal-mean )<br>0.97-4.83 (personal-range) | Italy | Petrucci *et al.*,2005 |

### 2.9.1 Mines

A small number of data concerning the air levels of platinum in mines have been available. Johnson *et al.* (1976) collected air samples during underground mining and in the building (where the metals were removed from the crushed ore slurry) from mines in the Sudbury area in Canada. The indicated platinum concentrations were very low and varied between <0.003 μg/m$^3$ (detection limit) and 0.4 μg/m$^3$ (Lindell, 1997; Health Council of the Netherlands, 2008).

### 2.9.2 Platinum refineries

The platinum air levels in refineries varied between 0.01-80000 μg/m$^3$. Shi (1987) reported extremely high levels of platinum (5000-80000 μg/m$^3$) in a badly ventilated platinum refinery in China, where the workers were exposed to complex platinum salts and platinum metal in the form of dust or spray. The average platinum concentration was below 10000 μg/m$^3$ at most places measured (Lindell, 1997; Health Council of the Netherlands, 2008).

Johnson *et al.* (1976) carried out another study sampling for 5 days in a typical refinery in New Jersey and reported platinum air concentrations between 0.02-0.26 μg/m$^3$ (mean: 0.16 μg/m$^3$) in the refinery section and 0.13-0.21 μg/m$^3$ (mean: 0.18 μg/m$^3$) in the salts section

Very low platinum air levels were found in two German studies and the concentrations ranged between <0.05 μg/m$^3$ (detection limit) and 2.0 μg/m$^3$. In the first study, Bolm-Audorff *et al.* (1992) stated that 2.0 μg/m$^3$ was maintained over the long term. However, two stationary air samplers measuring total dust for 2 hours in the separation shop showed platinum salt concentrations of 0.08 μg/m$^3$ and 0.1 μg/m$^3$. Two personal air samplers carried by filter press workers for 1 hour showed levels <0.05 μg/m$^3$ (detection limit). Alkaline dissolution of metallic platinum and manufacture of catalysts are processes considered to have relatively low or moderate exposure to platinum, while platinum refinery showed relatively high exposure. In the second study (Merget *et al.*, 1988) platinum salt exposure in the different working areas was generally below 0.08 μg/m$^3$, however, high exposure during the drying process of the salts was measured. No further details on the measurements were available (Lindell, 1997; Health Council of the Netherlands, 2008).

Fothergill *et al.* (1945) and Hunter *et al.* (1945) investigated four British refineries. Air levels of 0.9-1700 μg Pt/m$^3$ were reported. The majority of the refining operations (wet processes and/or local exhaust ventilation), showed levels less than 5 μg Pt/m$^3$. High levels of platinum (up to 1700 μg/m$^3$) were measured during the crushing of ammonium hexachloroplatinate(IV) (Lindell, 1997; Health Council of the Netherlands, 2008).

The HSE (1996) stated that about 96% of 8-hour TWA exposure measurements at refining and catalyst manufacture were well below the OEL of 2 μg/m$^3$ (calculated from measurements of exposure not available). Most of the exposures above 2 μg/m$^3$ occurred during the production and dispensing of soluble platinum salts. However, when the results were noted without reference to time-weighing there were a higher percentage of results (10%) above 2 μg/m$^3$.

Data relating to exposures of 1-4 hours indicated numerical values greater than 7-8 fold the OEL (2 μg/m$^3$) for the duration of the sampling period. HSE (1996) found that there was also a wider range of production areas which gave rise to these results, including process catalyst production, platinum recovery and platinum refining

Maynard *et al.* (1997) performed a study in the United Kingdom where soluble platinum concentrations were measured on two consecutive days at three different plants where three different processes were undertaken that is platinum refining, manufacture of platinum catalysts and metal-coated electrodes. In all cases, two different personal air samplers were used which included an IOM and CIP 10 personal sampler. On each of the 2 days, four workers wore both devices; one designated for ósshort-termô(generally 15 minutes) and the other for ólong-termô(6 - 8 hours) sampling while the designations were reversed the second day.

At the refinery where platinum and other precious metals were recovered, the measured ósshort-termôlevels (n=35) ranged from 0.01-26 μg/m$^3$. Twenty percent of these measurements were above the OEL of 2 μg/m$^3$. The 8-hour levels (n=8) ranged from 0.06-13.6 μg/m$^3$ and two measurements (25%) exceeded the OEL (Maynard *et al.*, 1997).

The following two plants, although not classified as refineries, will be included in this section given that they are part of this study. The plant involved in the production of platinum catalysts showed ósshort-termôairborne soluble platinum levels (n=35) between 0.02-10.82 μg/m$^3$. Ten percent of these measurements were above the OEL. The 8-hour levels (n=8) ranged from 0.03-0.6 μg/m$^3$. None of the ólong-termômeasurements were above the OEL (Maynard *et al.*, 1997). The plant, which produced metal-coated electrodes, ósshort-termôlevels (n=32) were between 0.03-0.99 μg/m$^3$ (75% <0.03 μg/m$^3$). The ólong-termôlevels (n=7) ranged from 0.003-0.079 μg/m$^3$. None of the measurements at this plant (ósshort or long-termô) exceeded the OEL (Maynard *et al.*, 1997)

### 2.9.3 Platinum recycling industry

Available data from the recycling industry reported platinum levels between 0.4-71 μg/m$^3$. A study carried out in America from 1977-1979 measured platinum salt air levels (>75 air measurements) in a plant that recovers platinum and other precious metals from scrap metals and expended catalysts. High levels of platinum salts were reported in the recovery, refinery and warehouse areas with a mean 8h-TWA air concentration exceeding the OEL between 50-75% of the time within a four-month period of measurements (Baker *et al.*, 1990; Brooks *et al.*, 1990; Health Council of the Netherlands, 2008).

An unpublished Swedish report (Gerd Sällsten, personal communication 1996 cited in the Health Council of the Netherlands, 2008), stated personal platinum exposures of between 15-71 μg/m$^3$ (197-305 min) for one worker during recycling of platinum catalysts (cutting and draining) and levels below 1 μg/m$^3$ for workers performing general duties.

In a French study, Hery *et al.* (1994) assessed the exposure of workers to metallic catalyst dust. Mostly metals other than platinum were measured, but one workersô personal exposure to platinum was sampled for 3 days and reported to be between 40-240 μg/m$^3$. This subject worked at a precious catalysts reprocessing plant, where metals were recovered by the destruction of spent catalysts (Health Council of the Netherlands, 2008).

### 2.9.4 Platinum metal using industry

The platinum levels in the platinum metal using industry were noted to be between 0.3-19.9 μg/m$^3$. Schaller *et al.* (1992) investigated the platinum metal using industry and measured the total platinum concentration in air utilising stationary and personal sampling at several working sites (no details were given). The levels noted ranged between 0.3-19.9 μg/m$^3$ (median 3.1 μg/m$^3$) during production of catalysts and 1.8-3.1 μg/m$^3$ (median 1.8 μg/m$^3$) during mechanical treatment (grinding, polishing, cutting and sawing) of platinum containing materials. A median value of 3.8 μg/m$^3$ was obtained in plants that recycle platinum catalysts (Health Council of the Netherlands, 2008).

### 2.9.5 Car catalyst manufacturing

From available data it is found that the platinum levels in the car catalyst manufacturing industry ranged between 0.005-3.7 μg/m$^3$. In a Swedish study, Granlund (1991) (cited in Health Council of the Netherlands, 2008) investigated platinum exposure during the manufacturing of car catalysts. A solution containing hexachloro-platinic(IV) acid and rhodium chloride (5:1) was used for the manufacture of catalysts.

Personal sampling was undertaken during the preparation of the platinum/rhodium solution, analytical work, coating of catalysts in the box and during packing of catalysts. The levels were found to be <0.2 μg/m$^3$ (below detection limit). Similar levels (<0.2 μg/m$^3$) were found when stationary sampling was used to measure the platinum air levels during the coating of the catalysts with the platinum/rhodium solution and during packing of the catalysts. Levels of <0.4 μg/m$^3$ were noted during the dilution of the platinum/rhodium solution (Health Council of the Netherlands, 2008).

In 1992 and 1993 airborne platinum concentrations were measured at several areas in a catalyst-production plant in Germany. The area with the highest platinum levels reported in 1992 ranged from roughly 0.005-0.7 μg/m$^3$ with a median value of 0.014 μg/m$^3$ (16 measurements; sampling time: 12-17 hours). In 1993, the levels ranged from roughly 0.006-0.015 μg/m$^3$ (12 measurements) with a median value of 0.037 μg/m$^3$. Personal air sampling performed in 1993 yielded much higher levels and the concentrations ranged from roughly 0.05-3.7 μg/m$^3$ (22 measurements; 3 of them >2 μg/m$^3$; sampling time: 8 hours) with a median value of 0.177 μg/m$^3$. Concentrations of total platinum measured were noted to be 10-fold higher (Merget, 2000; Merget *et al.*, 2000; Merget and Rosner, 2001; Health Council of the Netherlands, 2008).

### 2.9.6 Manufacture of platinum-coated oxygen sensors

In a Japanese study Shima *et al.* (1984) measured the platinum concentrations in the air during the manufacture of platinum-coated oxygen sensors. The industrial process involved the application of 50% hexachloroplatinic(IV) acid solution to zirconia porcelain, reacting the acid with ammonia to form ammonium hexachloroplatinate(IV) and calcining this to form a thin film of platinum. The platinum concentration at the two electrodes ranged between 0.14-1.83 μg/m$^3$ with 48-hour averages of 0.46 μg/m$^3$ and 1.1 μg/m$^3$. Cleaning of the sensors involves exposure to fine dust of ammonium hexachloroplatinate(IV) at higher concentrations when compared to those in the workplace as a whole, but no quantitative values were given in the study (Lindell, 1997). Petrucci *et al.* (2005) measured platinum concentrations at an Italian plant utilising $PM_{10}$ airborne sampling (airborne particulate matter less than 10 μm in diameter). Area and personal devices were used to collect whole airborne samples in all departments. The plant produce, recover and recycle catalytic converters for the automotive traction and chemical industries. Based on personal air sampling, the highest concentrations were reported in the coating department, followed by the recycling service, the metal dissolution department, and the process catalyst department.

Platinum seemed to be associated mainly with the fine fraction (<10 μm) in the coating department and the recycling service, while in the other areas, about 50% of the platinum was associated with the coarse fraction (>10 μm). The highest percentages of soluble platinum were found in the coating (mean 30% of the total) and metal dissolution department (mean 25% of the total) with a mean concentration of 1.21 μg/m$^3$ (2.54 μg/m$^3$ total platinum and 0.67 μg/m$^3$ soluble platinum). The personal platinum exposure was 2.70 μg/m$^3$ (mean), which ranged between 0.97-4.83 μg/m$^3$ (Petrucci *et al.*, 2005; Health Council of the Netherlands, 2008)

## 2.10 TOXICOKINETICS

### 2.10.1 Absorption

Most toxicokinetic data on platinum are derived mainly from studies on rats and mice using platinum complexes. The physicochemical properties of the compounds and the route of administration determine the absorption of platinum compounds.

#### *2.10.1.1 Intravenous administration*

Following intravenous injection of 1064 μg potassium tetrachloroplatinate (total platinum: 500 μg/rat) into female Lewis rats, 50% of the total platinum was excreted within 10 days via the kidneys and urine and 41% via the bile and faeces. Excretion via the faeces occurred somewhat faster (60% within 1 day and 70% within 2 days) compared to via the urine, (40% within 1 day and 50% within 2 days) (Lindell, 1997; Health Council of the Netherlands, 2008).

#### *2.10.1.2 Intratracheal instillation and inhalation*

Moore *et al.* (1975c) performed an experiment in which rats inhaled different chemical forms of platinum (5-8 mg/m$^3$; for 48 minutes) and slight absorption was noted. Lung clearance was biphasic, with a fast clearance phase in the first 24 hours followed by a slow phase with a half-life of about 8 days. Ten days after exposure to radiolabelled platinum ($^{191}$Pt) tetrachloride, platinum sulphate, platinum dioxide, and platinum metal, the whole body retention of radiolabelled platinum was approximately 1%, 5%, 8%, and 6%, respectively, of the initial body burden. Retention data (Table 6) indicate that 28.2% of the platinum metal (insoluble) was retained in the lungs after 16 days compared to platinum oxide and platinum sulphate (soluble) with retention percentages of 17.9% and 4.4% respectively after 16 days. Most of the radiolabelled platinum was cleared from the lungs by mucociliary action, swallowed and excreted via the faeces. A small fraction of the radiolabelled platinum was detected in the urine, indicating that very little was absorbed in the lungs and the gastrointestinal tract. Highest levels of radioactivity were found in kidney and bone, suggesting some accumulation in these tissues (IPCS, 1991; Lindell, 1997; WHO, 2000).

Table 6. Percentage of initial lung burden retained with time in the lungs (Moore *et al.*, 1975c).

| Time (days) | Portion of Pt burden retained (%) | | |
|---|---|---|---|
| | Platinum metal | Platinum oxide | Platinum sulphate |
| 1 | 63.0 | 57.2 | 73.7 |
| 2 | 49.5 | 60.9 | 43.4 |
| 4 | 41.3 | 49.0 | 20.4 |
| 8 | 42.9 | 28.6 | - |
| 16 | 28.2 | 17.9 | 4.4 |

In a more recent study Artelt *et al.* (1999b) investigated the bioavailability of finely dispersed platinum, similar to that emitted from automobiles equipped with catalytic converters. The number of platinum-containing particles emitted is too low to collect sufficient amounts for animal studies. Therefore, a closely resembling model substance was synthesised, consisting of aluminum oxide particles Ò5 µm (mean: 1.3 µm) onto which platinum particles Ó4 nm were deposited ($Al_2O_3$/Pt) (Health Council of the Netherlands, 2008). *In vitro*, the solubility for $Al_2O_3$/Pt in pure water (0.4%) and in 0.9% sodium chloride (saline) (10%) was unexpectedly high compared to the very low solubility of platinum powder (diameter 200-600 nm) in saline (0.001%). The higher solubility was attributed to the ultrafine structure of $Al_2O_3$/Pt, given that an inverse relationship between the particles diameter and the solubility was found (Artelt *et al.*, 1999b; Health Council of the Netherlands, 2008).

Further, part of the model substance was washed with saline. This washing procedure appeared to decrease the in vitro solubility in saline (0.1%) with the smallest platinum particles being ólemovedô during this washing procedure. In the saline extracts, platinum(II) and platinum(IV) complexes (i.e., mainly tetrachloroplatinates and hexachloroplatinates) were found. The bioavailability of platinum from the model substance was studied by applying untreated and/or washed $Al_2O_3$/Pt to female Lewis rats. Intratracheal instillation of 2 and 10 mg/animal once (1-day, 7-day study) or 2 and 10 mg/animal twice (at day 0 and day 4; 28-day, 90-day study), and by inhalation of 4 and 12 mg/m$^3$, 5 hours/day, 5 days/week, for three months (see Table 4). Flow rate, temperature, and aerosol concentration were continuously recorded in the inhalation study. The mass median aerodynamic diameter (MMAD) of the aerosols was determined to be 1.3 µm. Platinum contents of the liver, spleen, kidney, adrenals, stomach, femur, and lung (and bronchoalveolar lavage (BAL) cells and supernatant), blood, urine, and faeces were analysed (Artelt *et al.*, 1999b; Health Council of the Netherlands, 2008). The bioavailability was expressed as A x 100/(A+B). A represents the total platinum content in urine and all organs except the lungs. B represents the retained platinum in the ótotalô lung (including the lungs, BAL cell sediment and supernatant). Following inhalation of washed $Al_2O_3$/Pt complex, the bioavailability was 23% for the high concentration (12 mg/m$^3$) and 31% for the low concentration (4 mg/m$^3$).

Following instillation, the bioavailability was 4% at day 1, reaching values of 11-12% at post-instillation day 7 and 9-16% at day 28 and 90. The bioavailability of the washed compound and the platinum powder was lower, as could be expected from the lower *in vitro* solubility (see Table 7). However, the actual bioavailability might be higher. In these experiments, large amounts of platinum were found in the faeces. It was thought that this was the result of mucociliary clearance and subsequent ingestion of the particles and passage through the gastrointestinal tract, and that hardly any platinum becomes bioavailable via the gastrointestinal tract as was suggested in concomitant oral experiments.

Table 7. Bioavailability of platinum in female Lewis rats after intratracheal instillation and inhalation [a] (Artelt *et al.*, 1999b).

| $Al_2O_3$/Pt | dose | | Study duration | | | |
|---|---|---|---|---|---|---|
| | pt powder | platinum | 1 day | 7 days | 28 days | 90days |
| | | intratracheal instillation [b] | | | | |
| 20 mg untreated | | 620 µg | | | 12.0% | 8.5% |
| 20 mg washed | | 540 µg | | | 3.9% | 3.3% |
| 10 mg untreated | | 310 µg | 4.1% | 0.85% | | |
| 10 mg washed | | 270 µg | 11.0% | 3.1% | | |
| 4 mg untreated | | 128 µg | | | 16.2% | 13.5% |
| 4 mg washed | | 108 µg | | | 6.7% | 7.2% |
| 2 mg untreated | | 62 µg | 4.2% | 11.8% | | |
| 2 mg washed | | 54 µg | 0.6% | 3.4% | | |
| | 0.6 mg | 600 µg | | | 0.42% | 0.77% |
| | 0.3 mg | 300 µg | 0.045% | 0.21% | | |
| | | | inhalation [c] | | | |
| 4 mg/m$^3$ washed | | 160 µg | | | | 31.4% |
| 12 mg/m$^3$ washed | | 490 µg | | | | 22.7% |

a, Bioavailability after intratracheal instillation or inhalation is expressed as: A x 100/(A + B) with A = total platinum content in urine and all organs examined except the lungs and B = platinum retained in ótotalô lung, i.e., lungs + BAL cell sediment + supernatant; b, Test compound was instilled once in the 1 and 7-day study and in 2 equal aliquots at day 0 and day 4 in the 28 and 90 day study; c, Rats were exposed 5 hours/day, 5 days/week, for 3 months.

### *2.10.1.3 Oral administration*

When rats were given a single oral dose of 10 mg of $Al_2O_3$/Pt (via the diet) the bioavailability was calculated to be 0.1%, based on the distribution of platinum in various body tissues, blood, urine, and faeces. Gastrointestinal absorption has been studied to some degree in animal experiments, however, little uptake has been reported. In one study performed by Moore *et al.* (1975a, 1975b) less than 1% of the initial dose of platinum(IV) chloride (25 mCi) were absorbed through the gastrointestinal tract. Studies by Holbrook *et al.* (1975) and Lown *et al.* (1980), concerning blood levels and organ distribution of platinum, in small rodents after administration of platinum compounds showed peroral absorption, but no percentages were given. Accumulation of platinum occurred primarily in the kidney, where it was about 8 fold higher than in liver or spleen and 16 fold higher than in blood.

In contrast, when insoluble platinum oxide was given, only minute amounts were absorbed even though administered at a very high level. In this study, there was suggestive evidence of the induction of a platinum-binding protein. Peroral uptake of platinum is probably dependent on the particle size, since the study by Bader *et al.* (1992) (cited in Health Council of the Netherlands, 2008) on platinum metal illustrated that the administration of smaller particles (0.5 mm) led to a higher platinum retention than larger particles (150 mm). In contrast to the small peroral uptake of platinum compounds indicated by animal studies, large peroral uptake of platinum in humans was reported from a study carried out by Vaughan and Florence (1992).

The amount of platinum excreted in urine during the first 24 hours was found to represent at least 42% of the platinum in a hypothetical diet for an adult male. Further studies with more subjects receiving diets with known platinum contents would be necessary to make conclusions that are more reliable on uptake (Health Council of the Netherlands, 2008).

*2.10.1.4 Dermal administration*

No quantitative data on dermal absorption have been found. In one study performed by Roshchin *et al.* (1984), dermal application of ammonium chloroplatinate and a palladium compound reduced the body-mass gain in the research animals (species not given). After the termination of the trial, platinum was found in all internal organs examined as well as in urine and blood. Taubler (1977) performed a skin sensitisation study on guinea pigs and rabbits for EPA. No platinum could be detected in urine, serum or spleen, following repeated dermal application of 0.1 g or 0.25 g platinum(IV) sulphate, therefore suggesting little or no dermal absorption of this platinum salt. However, it must be noted that the platinum level in spleen was assessed about 14 days after the last application of platinum paste and the skin test procedure (Lindell, 1997; Health Council of the Netherlands, 2008).

**2.10.2 Distribution**

Studies have demonstrated that the route of administration determines the distribution and retention of platinum. In a study including male rats (Charles River CD-1) the whole-body retention of radiolabelled platinum (platinum(IV) chloride; single exposure) has been shown to decrease in the following order: intravenous (highest retention), inhalation and oral (Moore *et al.*, 1975a, 1975b, 1975c). The attainment of maximum platinum levels among different organs/tissues differs over time and the distribution of platinum compounds also changes with dose, with the greatest accumulation shown in the kidneys (Holbrook *et al.*, 1975; Lown *et al.,* 1980; Moore *et al.*, 1975a, 1975b, 1975c; Reichlmayr-Lais *et al.*, 1992).

*In vitro* studies demonstrated protein binding of ammonium tetrachloroplatinate(II) and potassium tetrachloroplatinate(II) to serum albumin and transferrin (Gauggel *et al.*, 1993; Sykes *et al.*, 1985; Trynda and Kuduk-Jaworska, 1994). In human blood samples most of the platinum was found to be associated with protein and about 65-80% of the platinum was found to be located in the erythrocytes (Vaughan and Florence, 1992). Erythrocytes were also found to contain more platinum than the plasma in a study where platinum(IV) chloride was administrated perorally to Sprague-Dawley female rats (Health Council of the Netherlands, 2008).

*2.10.2.1 Intravenous administration*

Following intravenous administration of radiolabelled platinum to rats, radioactivity was found in all tissues analysed during the first week, with the largest amount in the kidney and the lowest amount in the brain (Table 8). The high concentration of radioactivity found in the kidney (day 1: 6.65% per gram) shows that once platinum is absorbed most of it accumulates in the kidney after which it is excreted in the urine. The liver, spleen, and adrenal gland also contained higher platinum concentrations than the blood. The low radioactivity levels found in the brain indicated that platinum ions cross the blood-brain barrier only to a limited extent (Moore *et al.*, 1975a, 1975b). Decreased platinum levels were found in tissue where the blood concentration was also declined; therefore a relationship between platinum distribution and blood concentration can be suggested (Moore *et al.*, 1975a, 1975b).

This was confirmed by a study conducted by Lown *et al.* (1980) where male Swiss mice were given single intragastric doses of platinum(IV) sulphate (144 or 213 mg Pt/kg body weight). Platinum levels in the blood were several times higher than in the brain. Clearance from the whole body was slower than in the rat studies. This could be due to species-specific differences.

In addition, the mice received much higher doses than the rats. In addition, Lown *et al.* (1980) noted an increased absorption effect with the higher doses given to the mice. Following ten days of an intravenous injection of 1064 μg potassium tetrachloroplatinate(II) (total platinum: 500 μg/rat) to female Lewis rats, 8% of the total platinum recovered was distributed among the organs (no details presented) (Artelt *et al.*, 1999b)

Table 8. Radioactive $^{191}$Pt distribution (counts/g wet weight) in the rat following a single intravenous dose of platinum(IV) chloride (25 µCi/animal) (Moore *et al.*, 1975a)

| Tissue | 1 day | | 2 day | | 7 day | | 14 day | |
|---|---|---|---|---|---|---|---|---|
| | %/g | counts/g | %/g | counts/g | %/g | counts/g | %/g | counts/g |
| Blood | 0.91 | 22 147 | 0.81 | 19 732 | 0.52 | 12 774 | 0.32 | 7 921 |
| Heart | 0.48 | 11 819 | 0.50 | 12 201 | 0.36 | 8 805 | 0.19 | 4 593 |
| Lung | 0.75 | 18 432 | 0.66 | 16 139 | 0.46 | 11 180 | 0.24 | 5 770 |
| Liver | 1.51 | 36 848 | 1.28 | 31 274 | 1.05 | 25 732 | 0.19 | 4 733 |
| Kidney | 6.65 | 162 227 | 6.59 | 160 656 | 5.66 | 138 010 | 1.24 | 30 195 |
| Spleen | 1.68 | 41 085 | 1.89 | 45 840 | 2.29 | 55 764 | 0.86 | 20 973 |
| Pancreas | 0.91 | 22 208 | 0.80 | 19 487 | 0.60 | 14 802 | 0.16 | 3 973 |
| Bone | 0.53 | 13 146 | 0.52 | 12 800 | 0.37 | 8 932 | 0.22 | 5 440 |
| Brain | 0.05 | 1 150 | 0.10 | 2 485 | 0.02 | 595 | 0.01 | 265 |
| Fat | 0.18 | 4 487 | 0.18 | 4 501 | 0.13 | 3 201 | 0.02 | 429 |
| Testes | 0.17 | 4 186 | 0.27 | 6 540 | 0.16 | 3 873 | 0.06 | 1 431 |
| Adrenal | 1.86 | 45 439 | 1.74 | 42 363 | 1.09 | 26 667 | 0.25 | 6 190 |
| Muscle | 0.19 | 4 798 | 0.19 | 4 671 | 0.14 | 3 441 | 0.09 | 2 146 |
| Duodenal segment | 0.52 | 12 725 | 0.25 | 6 044 | 0.16 | 4 031 | 0.06 | 1 410 |

*2.10.2.2 Inhalation exposure*

Moore *et al.* (1975c) performed a study on male rats (Charles River CD-1) where they were exposed to radiolabelled platinum or platinum oxide via inhalation (7-8 mg/m$^3$; 48 min; particle size not given). It was shown, that the initial lung burdens for radiolabelled platinum metal and platinum oxide represented about 14% and 16% of the initial body burdens. Most of the radioactivity had been eliminated from the gastrointestinal tract within 24 hours, while the lung still contained about 60% of the initial lung burden (Table 6).

In addition to the lungs (day 1: 45462 counts/g) and trachea (day1: 1909 counts/g), the kidneys (day1: 750 counts/g) and bones (day 1: 281 counts/g) were found to contain the highest concentrations of radioactivity when radiolabelled platinum was counted in selected tissues 1-8 days after exposure (Table 9).

The brain contained very small amounts of radiolabelled platinum (1day: 5 counts/g). When exposed by inhalation to 12 mg/m$^3$ of washed $Al_2O_3$/Pt (see Section 5.1.2), 5 hours/day, 5 days/week, for three months, only 0.01% of the total platinum was recovered from the organs (liver, spleen, kidneys, adrenals, stomach, femur) with highest amounts in the liver (0.13 µg) and the kidneys (0.042 µg). Following inhalation of 4 mg/m$^3$, only 0.003% was recovered with the highest amount in the kidney (0.016 µg) (Artelt *et al.*, 1999b)

Table 9. Radioactive $^{191}$Pt in selected tissues following inhalation exposure to platinum metal (Moore *et al.*, 1975c).

| Tissues | Days after exposure | | | |
|---|---|---|---|---|
| | 1 | 2 | 4 | 8 |
| Blood | 61* | 43 | 30 | 12 |
| Trachea | 1909 | 2510 | 738 | 343 |
| Lung | 45462 | 28784 | 28280 | 23543 |
| Liver | 52 | 46 | 37 | 17 |
| Kidney | 750 | 1002 | 906 | 823 |
| Bone | 281 | 258 | 231 | 156 |
| Brain | 5 | 3 | 1 | 0 |
| Muscle | 22 | 10 | 28 | 0 |
| Spleen | 39 | 73 | 23 | 5 |
| Heart | 37 | 58 | 23 | 5 |

*mean counts per gram

*2.10.2.3 Oral administration*

In a long-term study, Bader *et al.* (1992) and Bogenrieder *et al.* (1993) (cited in Health Council of the Netherlands, 2008) orally administered platinum salts to male Sprague-Dawley rats, either in their drinking-water or dry feed. Peroral administration to rats has shown, that administration of a water-soluble platinum salts such as platinum(IV) chloride leads to much higher concentrations of platinum in the blood and tissues, than administration of platinum metal (at comparable doses), but the particle size has been found to influence the concentration of platinum metal, especially in the kidneys (IPCS, 1991; Health Council of the Netherlands. 2008).

In these and other animal experiments the absorbed platinum (orally given platinum metal, platinum(II) chloride, platinum(IV) chloride or platinum(IV) sulphate) was distributed to virtually all organs and tissues, with the highest amounts of absorbed platinum found in the kidneys, while low levels have been found in the adipose tissue and brain (Moore *et al.*, 1975a,1975b; Lown *et al.*, 1980; Reichlmayr-Lais *et al.*, 1992).

*2.10.2.4 Subcutaneous administration*

In a study conducted by Zhong *et al*. (1997a, 1975b) it was found that metallothionein synthesis in the liver and kidney were induced when disodium hexachloroplatinate was subcutaneously administrated to rabbits. Hepatic metallothionein contained small amounts of platinum (0.04 g atom/mol protein), whereas renal metallothionein contained higher platinum amounts (2.6 g atom/mol protein). The oxidation state of platinum in metallothionein was found to be +2 and this results suggested that platinum(IV) complexes may be reduced *in vivo* to platinum(II) compounds that bind to metallothionein. This process may play a significant role in reducing the cytotoxicity of platinum(IV) complexes.

*2.10.2.5 Human tissue platinum content*

Studies conducted from the early 1965's (Wester, 1965) have examined the platinum levels in human tissue from humans not occupationally exposed to platinum compounds. It was found that the platinum levels varied greatly and ranged from 0.005-1170 ng/g wet weight and included tissue from the liver, kidney, spleen, lung, heart, muscle, brain and fat (Duffield *et al.*, 1976; Johnson *et al.*, 1976; Zeisler and Greenberg, 1988; Yoshinaga *et al.*, 1990). Earlier findings were confirmed by Benes *et al.* (2000) that reported a great variation in the platinum content of human tissues. In 70 autopsied individuals (54 males, 16 females; age: 18-76 years) from the North Bohemia territory of the Czech Republic, the platinum content in liver, kidney, and bone was found to be in the range of 2-3920 μg/kg (median: 2 μg/kg), 2.5-750 μg/kg (median: 2.5 μg/kg), and 10-230 μg/kg (median: 10 μg/kg) wet weight, respectively. No significant differences were seen between males and females.

*2.10.2.6 Foetal uptake and distribution*

Foetal uptake of platinum compounds has been investigated in a few studies and was reported to be very low. In one study (Moore *et al.*, 1975a) pregnant rats where given 25 μCi radiolabelled platinum(IV) chloride intravenously and very low levels of the platinum were present (after 24 hours) in all the foetuses measured, with 0.01% of the dose/g in whole foetal tissue, 0.05% of the dose/g in foetal liver and 0.9% of the dose/g in placental tissue (Lindell, 1997).

In another study in rats, platinum(IV) chloride or platinum metal was administered from four weeks before pregnancy to the twentieth day of gestation (Kirchgessner *et al.*, 1992,1993; cited in Lindell,1997). The platinum was given in the diet in five different concentrations up to 100 mg/kg diet. Platinum levels found in the uterus and in the foeto-placental unit generally was much higher in the platinum(IV) chloride groups compared to the corresponding PGMs, but still represented a very small part of the ingested amount of platinum. The highest platinum levels in the foeto-placental unit were found in the amnion, where about 80-90% of the measured platinum was situated. Platinum concentrations were lowest in the foetuses from the groups given 50 mg/kg and 100 mg/kg platinum(IV) chloride. When platinum(IV) chloride or platinum(II) chloride was given to lactating rats in concentrations of 50 mg/kg and 100 mg/kg diet only platinum(IV) chloride was detected in the milk, while platinum(IV) chloride as well as platinum(II) chloride (at 50 mg/kg and 100 mg/kg levels) were found in the carcass of the offspring after administration. The platinum levels in the offspring was found to be highest at the end of the lactation period and generally higher in the offspring after administration of platinum(IV) chloride (Kirchgessner *et al.*, 1993; cited in Lindell,1997).

### 2.10.3 Elimination

*2.10.3.1 Intravenous*

Following intravenous administration of radiolabelled platinum(IV) chloride to male rats (Charles River CD-1), the majority of the radioactivity was excreted into the urine and a lesser amount into the faeces. After 3 days, 35% of the platinum was excreted and after 28 days, 86% was eliminated (Moore *et al.*, 1975b). Following intravenous injection of 1064 µg potassium tetrachloroplatinate (total platinum: 500 µg/rat) into female Lewis rats, 50% of the total platinum were excreted within 10 days via the kidneys and urine and 41% via the bile and faeces. Excretion via the faeces occurred somewhat faster (60% within 1 day and 70% within 2 days) compared to via the urine, (40% within 1 day and 50% within 2 days) (Lindell, 1997; Health Council of the Netherlands, 2008).

*2.10.3.2 Inhalation*

Following inhalation by male rats for 48 minutes to several labelled platinum salts (platinum(IV) chloride, 5.0 mg/m$^3$; platinum(IV) sulphate, 5-7 mg/m$^3$; platinum(IV) oxide, 7-8 mg/m$^3$; or platinum metal, 7-8 mg/m$^3$), most of the radiolabelled platinum was excreted via the faeces during the first days; only small amounts were present in the urine (faeces:urine ratio was not reported). Clearance appeared to be biphasic: an initial rapid phase was followed by a slower second phase. After 24 hours, 20-40% of the initial body burden of radioactivity was excreted, while after 10 days more than 90% had been excreted (Moore *et al.*, 1975c)

*2.10.3.3 Perorally*

In a study where radiolabelled platinum(IV) chloride was administered perorally to male rats (Charles River CD-1) most of the radioactive platinum was eliminated in the faeces and only a small amount was excreted in the urine, suggesting that the majority had passed the gastrointestinal tract unabsorbed (Moore *et al.* 1975a,1975b).

*2.10.3.4 Excretion in humans*

Excretion in humans has been estimated to some extent and limited data indicate slow elimination of platinum metal. In one study with a few platinum workers, no evident difference were found in the platinum levels before and after an exposure-free period (15 days), when platinum was measured in the urine and serum of four workers occupationally exposed to platinum metal. In agreement with this, increased platinum levels were found in the urine of one worker exposed to platinum during recycling of platinum catalysts (cutting, draining), while no definite decrease in urinary platinum levels were seen during an unexposed period (at least 12 days) (Lindell, 1997; Health Council of the Netherlands, 2008).

The urinary excretion of platinum was estimated in one adult male from Sydney, not occupationally exposed to platinum compounds, and was found to be between 0.76-1.07 mg/day (Vaughan and Florence, 1992). However, the urinary platinum levels obtained in this study are very high compared to the levels obtained by some other authors (see section 2.11 biological monitoring).

In a study performed by Schierl *et al.* (1998) urinary excretion in humans was examined. Thirty-four workers, 32 men and 2 women, from a platinum refinery and catalyst production company were divided into four groups: group 1, current high exposure (mainly potassium tetrachloroplatinate and platinum nitrate;); group 2, former high exposure (exposure eliminated 2-6 years ago because of hypersensitisation); group 3, current low exposure (only occasionally exposed to lower levels) and group 4, the control group (no exposure). Sampling always included two spot urine samples, one at the end of a shift at the plant and a second one the next morning at home. It was found that the urinary platinum levels were highest in group 1 followed by group 2, 3 and 4 in decreasing order. For group 1, air platinum concentrations ranged from 0.2-3.4 $\mu g/m^3$ (stationary: mean 1.1 $\mu g/m^3$) and from 0.8-7.5 $\mu g/m^3$ (personal air sampling: mean 2.5 $\mu g/m^3$). Employees not exposed for several years (group 2) and free from symptoms still excreted 25 fold more platinum than the control group, indicated that platinum may accumulate in the body. Platinum excretion in occasionally exposed workers (group 3) was closer to the control group showing a 3-40 fold increase after a shift and a 3-8 fold increase the next morning. For the control group, concentrations were <0.007 $\mu g/m^3$. For group 1, the urinary platinum excretion after a shift increased 1000-6270 ng/g creatinine where it increased to a lesser extent in the morning (500-2620 ng/g creatinine). Schierl *et al.* (1998) investigated the excretion kinetics of platinum in more detail by exposing two human volunteers via inhalation to ammonium hexachloroplatinate(IV). Person A was exposed to 0.15 $\mu g/m^3$ and person B to 1.7 $\mu g/m^3$ ammonium hexachloroplatinate(IV), respectively. The amount of platinum measured (4 hours) on filters in the breathing zone was lower for person A: (60 ng) compared to person B (800 ng) Platinum excretion was measured in all urine that were sampled the first four days and in samples taken less frequently in the next 4 months. The excretion of platinum showed to be rapid and dependent on exposure concentration. A steep increase (15-100 fold) in urinary platinum was found reaching its maximum nearly 10 hours after inhalation with 23 ng/g creatinine in person A and 520 ng/g creatinine in person B. Only in the case of high platinum exposure (person B), the clearance was biphasic with a half-live of 50 hours (95% confidence interval: 36-66 hours) calculated for both subjects while a second half-life of 24 days (95% confidence interval: 18-33 days) was found for person B. Data on biotransformation of platinum or platinum salts were not available (Schierl *et al.*, 1998).

## 2.11 BIOLOGICAL MONITORING

Reference values of platinum in blood and urine have been projected in some studies in recent years, but substantial variation has been observed in the results obtained by different authors as illustrated in Table 10 (Health Council of the Netherlands, 2008). These large differences in platinum levels in urine and blood might partly be due to differences and difficulties in analytical methodologies. Due to analytical problems and difficulties in establishing a reference value for platinum in blood and urine no method can until now be applied routinely for the monitoring of platinum. Methods based on AV are extremely sensitive, but must be further assessed before it can be effectively utilised in practice. Most other available analytical methods are not sensitive enough to monitor low levels of platinum in occupationally exposed workers. Background levels of platinum are suggested to be in the order of <0.8-7 ng/L in blood and 0.5-15 ng/L in urine with a significant correlation between levels in blood, serum, and urine (Messerschmidt *et al*., 1992; Ensslin *et al.*, 1994). Other reports indicate much higher platinum levels in blood and urine of occupationally exposed people: in the order of magnitude of 500-1800 ng/L in blood and 250 ng/L in urine, but doubts have arisen as to the reliability of these analyses (Johnson *et al*., 1975; Nygren *et al.*, 1990, 1991; Vaughan and Florence, 1992).

A study performed by Schaller *et al.* (1992) on 40 occupationally exposed workers showed mean platinum levels of 39 ng/L (in the blood and serum) in the production section and 125 ng Pt/L in the blood and 75 ng Pt/L in the serum, in the mechanical treatment section. Urine levels were 1260, 330, and 430 ng/L in the people of the production, recycling, and mechanical treatment section, respectively. There was a significant correlation between levels in blood, serum, and urine, but not with the median concentrations in air, which were reported to be 3.1, 3.8, and 1.8 μg/m$^3$ in the production, recycling, and mechanical treatment section, respectively (Schaller *et al.*, 1992).

Farago *et al.* (1998) reported mean concentrations of platinum of 246 ng/L and of 470 ng/g creatinine in whole blood and urine, respectively, in seven platinum refinery workers, compared to levels of 145 ng/L and 58 ng/g creatinine and of 129 ng/L and 113 ng/g creatinine in ten motorway maintenance workers and five university staff, respectively. There was a significant correlation between the blood and urine levels.

Petrucci *et al.* (2005) evaluated occupational exposure in an industrial plant in Italy engaged in the production, recovery, and recycling of catalytic converters for the automotive traction and chemical industry. The highest concentrations of platinum were found in the coating department with mean levels of 2.70 μg/m$^3$ (range: 0.97-4.83 μg/m$^3$) in personal air samples.

The corresponding mean concentrations in blood, urine and hair were 0.38, 1.86 and 2.26 µg/kg, respectively. Workers from departments with lower exposure levels had correspondingly lower platinum levels in urine, blood, and hair. Employees from departments with no direct exposure still had blood and urine levels that were about 20 times higher than those of unexposed controls living in a rural area (i.e., 0.01 and 0.005 µg/l, respectively). Petrucci *et al.* (2005) concluded that the differences in exposure as measured by personal air sampling were best reflected by the platinum levels found in the urine. Other studies also demonstrated that platinum levels in blood and, especially, urine are good indicators of exposure to platinum.

Table 10. Reference values of platinum in blood, urine and workplace air samples taken in various types of industries (Health Council of the Netherlands, 2008).

| Industry | n | Blood | Urine ng/L | Air ug/m$^3$ | Country | Study |
|---|---|---|---|---|---|---|
| Community residents (Baseline) | 21 | 600 ng/L | 250 ng/L | | Sydney | Vaughan and Florence, 1992 |
| Community residents (Baseline) | 10 | 580 ng/L | | | Sweden | Nygren *et al.*, 1991 |
| Community residents (Baseline) | 18 (bl)<br>11 (ur) | 590 ng/L | 110 ng/L | | Sweden | Nygren *et al.*, 1990 |
| Community residents Near freeway | | 490 ng/L | | | California | |
| Community residents High desert area | | 1800 ng/L | | | California | |
| Community residents (Baseline) | 13 (bl)<br>14 (ur) | <0.8-6.9 ng/L | 0.5-14.3 ng/L<br>3.5 ng/L (mean) | | Germany | Messerschmidt *et al.*, 1992 |
| Hospital personnel | 11 (ur) | | 2.1-15.2 ng/L<br>5.3 ng/L (mean) | | Germany | Ensslin *et al.*, 1994 |
| Platinum catalyst production | 40 | 2-180 ng/L<br>39 ng/L (mean) | 10-9200 ng/L<br>1260 ng/L (mean) | 3.1 | Germany | Schaller *et al.*, 1992 |
| Platinum catalyst recycling | 40 | 2-180 ng/L | 10-9200 ng/L<br>330 ng/L (mean) | 3.8 | Germany | |
| Platinum chemical treatment | 40 | 2-180 ng/L<br>125 ng/L (mean) | 10-9200<br>429 (mean) | 1.8 | Germany | |
| Platinum processing industry | 21 | 100-280 ng/L | 70-1350 ng/L<br>280 ng/L (mean) | 1.7-6.0 | Germany | Weber *et al.*, 1991 (cited in Health Council of the Netherlands, 2008) |
| Platinum recycling industry | 21 | 100-280 ng/L | 20-630 ng/L<br>320 ng/L mean) | 1.7-6.0 | Germany | |
| Platinum chemical treatment | 21 | 100-280 ng/L | 10-2900 ng/L<br>330 ng/L (mean) | 1.7-6.0 | Germany | |
| Platinum Refinery | 61 | <1.4 ng/g | 0.23-2.58 ug/L (p)<br>0.49-0.66 ug/L (r)<br>1.22-1.24 ug/L (s) | 0.16-0.18 | New Jersey | Johnson *et al.*, 1976 |
| Mining/ore processing | 49 | <0.0014 ug/g | <0.00002ug/g | <0.003 | Canada | |
| Production, recovery, and recycling of catalytic converters | | 380 ng/L | 1860 | 2.7 | Italy | Petrucci *et al.*, 2005 |
| Platinum refinery | 7 | 246 ng/L | 470 ng/g | | United Kingdom | Farago *et al.*, 1988 |
| Motorway maintenance workers | 10 | 145 ng/L | 58 ng/g | | United Kingdom | |
| University staff | 5 | 129 ng/L | 113 ng/g | | United Kingdom | |
| Platinum industry Highly exposed workers | 15 | | 1994 ng/g | 2.5 | Germany | Schierl *et al.*, 1998 |
| Platinum Industry Stopped working 2-6 years back | 4 | | 120ng/g | | Germany | |
| United States NHANES | 496 | | 1260 ng/g | | United States | Paschal *et al.*, 1998 |

bl, blood; ur, urine; n, Amount of samlpes taken; AV, Adsorptive Voltammetry; ICP-MS, Inductively Coupled Plasma Mass Spectrometry; p, refinery plant; r, refinery section; s, platinum salts section; NHANES, National Health and Nutrition Examination Survey

## 2.12 MECHANISM OF TOXICITY

### 2.12.1 Human studies

Detailed information regarding the onset and effects of platinum exposure is discussed in section 2.13. This section will mainly focus on the possible mechanism that causes toxicity. Platinum salt induced reactions of the respiratory tract and the skin reported in man are generally considered to be a Type I, Immunoglobulin E (IgE) mediated response (White and Cordasco, 1988; Lindell, 1997). The possibility of the formation of IgE antibodies to platinum chloride complexes in sensitised individuals has been assumed on the grounds of allergy and serological tests. It is believed that platinum salts of low relative molecular mass combine with serum proteins to form the complete antigen (act as haptens) which can provoke a specific immune response. However, the actual immunological mechanism has not yet been defined (Health Council of the Netherlands, 2008). Once sensitisation has developed, subsequent exposures to minute concentrations of the platinum salt have elicited both immediate (Type I) and delayed reactions (Type IV) (Kazantzis, 1990; Nakayama *et al.*, 1997).

Evidence that the sensitising potential of platinum compounds is restricted to the soluble halogenated compounds is accumulating. Linnett and Hughes (1999) evaluated 20 years of medical surveillance on exposure to platinum compounds and reported that for platinum compounds to be allergenic, a halide ligand coordinated to platinum is required. Chloroplatinates are clearly allergenic while non-halogenated and neutral complexes (halide present as an ion) have been shown to be nonallergenic.

Skin-prick tests with ammonium and sodium hexachloroplatinate and with sodium tetrachloroplatinate are used routinely in monitoring platinum workers to provide specific and sensitive indicators of an allergic state. Skin-prick tests with low ($10^{-9}$ g/ml) concentrations of these platinum compounds have produced immediate weal and flare reactions in highly sensitised individuals, but no reactions have been seen in atopic or non-atopic controls (Murdoch and Pepys, 1984, 1987).

The sensitivity and reliability of the skin-prick test has not been equalled by any other test. The *in vitro* radioallergosorbent test and tests for histamine release are too non-specific to be used for screening purposes. There is evidence, though limited, to suggest that bronchial hyperresponsiveness, as shown by the cold air challenge test, may precede evidence of cutaneous sensitisation in platinum-exposed workers (Dally *et al.*, 1980; Brooks *et al.*, 1990; O'Hollaren, 1992).

Raulf-Heimsoth *et al.* (2000, 2001) examined the molecular mechanisms involved by determining the T-cell receptor (TCR) expression, additional cell surface molecules, proliferation of peripheral blood mononuclear cells (PBMC), and cytokine production without and after *in vitro* stimulation with sodium hexachloroplatinate. It was found that platinum salt-sensitised workers had a significantly higher frequency of specific T-cells compared to non-exposed subjects. *In vitro* stimulation of PBMC from exposed workers and non-exposed controls with sodium hexachloroplatinate resulted in a time- and dose-dependent increase in specific T-cells.

The interaction of complex or simple salts of platinum with Deoxyribonucleic acid (DNA) has not been very well studied, but some soluble platinum salts like platinum(IV) chloride, platinum(IV) sulphate, potassium hexachloroplatinate(IV), potassium tetrachloroplatinate(II) and ammonium hexachloroplatinate (IV) have been found to be mutagenic/genotoxic *in vitro* (Kanematsu *et al.*, 1980, 1990). The above mentioned studies will be discussed in more detail in section 2.13.

### 2.12.2 Animal studies

Following animal studies it has been found that the acute toxic effects of platinum are dependent on metal speciation with the soluble platinum compounds being much more toxic, in particular the coordination complexes, compared to the metallic form.

Attempted sensitisation in experimental animals including monkey, dog, guinea-pig and rat has given conflicting results. Exposure to soluble platinum salts induced bronchoconstriction, anaphylactic shock, and elevated plasma histamine levels either systemically or locally (WHO, 2000). All tested platinum compounds have shown eye irritation, a number of compounds have caused skin irritation (in albino rabbits) and ammonium tetrachloroplatinate was found to be corrosive. Nasal inhalation of sodium hexachloroplatinate (in cynomolgus monkeys) caused pulmonary deficits compared with controls, while ammonium hexachloroplatinate produced pulmonary hyperreactivity and skin hypersensitivity but only with simultaneous exposure to ozone (Biagini *et al.*, 1985b, 1986).

Degussa (1989) reported that ammonium tetrachloroplatinate induces acute poisoning in rats, with hypokinesia, diarrhoea, convulsions and respiratory impairment. Ward *et al.* (1976) found that hexachloroplatinic acid is also highly nephrotoxic in rat. In contrast, metallic platinum orally administered to rats as fine particles produced minor necrotic changes in the gastrointestinal epithelium and swelling of the epithelium of the convoluted renal tubules, with no lethal effect proposing that the soluble form is more toxic when compared to the metallic form (IPCS, 1991).

Immunogenicity of soluble platinum salts was demonstrated in mice by means of the popliteal lymph node assay. Differences were noted in the degree of response between the various mouse strains used, and it was shown that mice deficient in T-lymphocytes completely failed to respond (Schuppe, *et al.*, 1992).

Testing the immune response in mice utilising platinum tetrachloride and hexachloride salts, the following effects were found: (a) stimulation of receptor-mediated endocytosis in Langerhans cells (b) stimulation of cell proliferation in lymph nodes (c) stimulation of Th2-type cytokine production (d) inhibition of Th1-type cytokine production (interferon-gamma) and (e) stimulation of anti-nuclear autoantibodies. These results confirm the sensitisation potential of soluble platinum salts with a halide ligand coordinated to platinum. The studies are outlined in more detail in Section 2.13 (Health Council of the Netherlands, 2008).

## 2.13 HEALTH EFFECTS

### 2.13.1 Observations in humans

*2.13.1.1 Irritation and sensitisation*

Occupational inhalation exposure to platinum salts (particularly the soluble types) leads to respiratory sensitisation and skin reactions (White and Cordasco, 1988; Rosner and Merget, 1990). Symptoms include lacrimation, irritation of the upper respiratory tract, rhinitis and coughing, as well as angioedema and urticarial and eczematous skin lesions. However, true allergic contact dermatitis from exposure to platinum compounds is rare and the dermatitis occasionally seen may be of a primary irritant nature e.g. following exposure to strong acids and alkalis (Boggs, 1985; Fisher, 1986; Linnett, 1987)

Platinum compounds mainly responsible for sensitisation are hexachloroplatinic(IV) acid and chloroplatinate salts such as ammonium hexachloroplatinate(IV), ammonium tetrachloro-platinate(II), potassium hexachloroplatinate(IV), potassium tetrachloroplatinat(II) and sodium hexachloroplatinate(IV) (Rosner and Merget, 1990). In a study with platinum-refinery workers with a known sensitivity to platinum(IV) chloride and hexachloroplatinic acid (oxidation state 2-), a number of platinum salts were tested using skin prick tests. The results demonstrated that a small group of charged complexes that contained reactive halogen ligands induced an allergy.
The chloroplatinates were highly allergenic with chloro ligands being most effective; changing from chloro to bromo ligands reduced the response, while neutral complexes or more strongly bound ligands with poor leaving abilities (such as nitro, thiocyanato and amine ligands) were immunologically inactive. In these tests, an immunological type I reaction has been established for the chloroplatinates (Cleare *et al*., 1976).

Tests performed by Biagini *et al.* (1985a) and Cromwell *et al.* (1979) also indicated an IgE-mediated reaction. Metallic platinum (insoluble type) is not associated with hypersensitivity, although a single case of dermatitis due to a platinum ring has been reported (Sheard, 1955).

The latency period from initial contact with platinum compounds to the development of symptoms has varied from a few weeks to several years (Merget *et al.*, 1988; Merget *et al.*, 1991). The symptoms tend to worsen with increasing length and intensity of exposure and sensitised individuals as a rule are never asymptomatic in a platinum-containing atmosphere. Following removal of subjects from the platinum-containing workplace the symptoms generally disappear, but there are descriptions of workers with a delayed response and nocturnal asthma, who have continued to experience symptoms for a few weeks after removal (Linnett, 1987). Furthermore, a nonspecific airway hyperreactivity may persist (Merget *et al.*, 1994).

Atopy does not appear to be a significant predisposing factor; therefore, atopic as well as non-atopic workers may be affected when exposed to platinum compounds (Brooks et al., 1990; Merget et al., 1988). It was established that tobacco smoking increases the risk of occupational exposed individuals towards the development of PSS (Calverley, *et al.*, 1995) since it increases the permeability of the respiratory epithelium. It has also been proposed that simultaneous exposure to irritants (like chlorine, ammonia, or ozone) potentiates the effects of PSS in a way similar to tobacco smoke (Baker *et al.*, 1990; Holt, 1987; Venables *et al.*, 1989). Several reports indicated a positive correlation between PSS and increased prevalence of rhinitis, asthma, and dermatitis symptoms (Baker *et al.*, 1990; Biagini *et al.*, 1985a; Bolm-Audorff *et al.*, 1992; Brooks *et al.*, 1990). Table 5 presents an overview of the prevalence of PSS in workers exposed to platinum salts.

Table 11. Prevalence of symptoms and positive skin tests in workers exposed by inhalation to soluble platinum salts (Health Council of the Netherlands, 2008).

| Total Workers[a] | Workers with symptoms (%) | Skin-tested workers[b] | Workers with positive skin test (%) | Pt concentration in air (μg/m$^3$) | Country | Reference |
|---|---|---|---|---|---|---|
| 91 (52) | 57 | 16 (4) | 25 | 0.9 - 1700 | UK | Hunter *et al.*, 1945 |
| 20 (12) | 60 | 19 (8) | 42 | nd | USA | Roberts, 1951 |
| 11 (8) | 73 | nd | nd | nd | Germany | Massmann and Opitz, 1954* |
| 16 (14) | 88 | nd | nd | nd | Germany | Sauerwald, 1961* |
| 51 (35) | 69 | nd | nd | nd | France | Parrot *et al.*, 1969 |
| 91 (49) | 54 | 84 (22) | 26 | nd | UK | Venables *et al.*, 1989 |
| 306 | - | 306 (38) | 12 | nd | SA | Murdoch *et al.*, 1986 |
| 107 (28as) (46rh) | 29as 44rh | 107 (15) | 14 | > 2 | USA | Baker *et al.*, 1990 Biagini *et al.*, 1985a Brooks *et al.*, 1990 |
| 24(2) | 8 | 20 (4) | 20 | < 0.08 | Germany | Merget *et al.*, 1988, 1991 |
| 65 (15) | 23 | 64 (12) | 19 | <0.1, < 2.0 [c] | Germany | Bolm-Audorff *et al.*, 1992 |

a, Values in parentheses are number of workers with symptoms; b, Values in parentheses are number of workers with a positive skin test; c, Air monitoring resulted in platinum concentrations of <0.2 μg/m$^3$ (1984); <0.1 μg/m$^3$ (1986) (< German OEL of 2.0 μg/m$^3$ );nd = not determined; as, asthma; rh, rhinitis; C; cited in Health Council of the Netherlands, 2008.

Hunter *et al.* (1945) published the first occupational survey conducted on platinum refinery workers, where measurements of the platinum content in the air were made. The authors investigated all workers (91) in four British refineries and in some cases attempted to test skin sensitivity (intradermally). Analysis of the symptoms showed that 13 men had skin lesions: urticaria or scaly erythematous dermatitis of hands, forearms and sometimes also face and neck. It was also stated that out of 91 men in contact with the complex salts of platinum, 57% had the asthmatic syndrome to some degree when in the refinery and it was noted that the symptom prevailed for about one hour after they had left the workplace. Sixteen of the workers were skin-tested and 25% of the workers had a positive skin test. Often these men also woke up early in the morning with a bout of coughing. The incidence of asthma was highest in those in contact with the complex salts in their dry form, but symptoms were also diagnosed in workers engaged in certain parts of the wet process, where droplets of the complex salts were present in the atmosphere. The platinum content of the air in the refinery atmosphere was estimated at various points and during various operations with figures ranging from 0.9-1700 $\mu g/m^3$. In one of the platinum refineries, where the concentration of platinum in the air was 0.9-3.2 $\mu g/m^3$, 5 out of 7 workers said they experienced sneezing and running of the nose for a short duration, when they were in contact with the complex salts of platinum for a few minutes at a time. No instances of asthma was noticeable in the workers exposed to metallic platinum dust only (insoluble form), in any of the factories, even though high concentrations of platinum in the atmosphere (400-960 $\mu g/m^3$) were reported during the sieving of the spongy platinum.

Roberts (1951) conducted a five-year study on refinery workers in the United States exposed to platinum salts and reported even higher occurrences of symptoms compared to the study performed by Hunter *et al.* (1945). All subjects (n=20) exhibited some level of inflammatory changes in the conjunctivae and the mucous membranes of the upper respiratory tract, while 60% were symptomatic (include e.g. burning and itching of eyes, tightness in throat and chest, dry cough, asthma, itching of skin, dermatitis). Nineteen of the men were also skin tested (scratch test) and 42% of them had a positive skin test. In two German studies (Massmann and Opitz, 1954; Sauerwald, 1961) (cited in Health Council of the Netherlands, 2008) work-related symptoms such as sneezing, coughing, asthma, urticaria and eczema were found. Massmann and Opitz (1954) studied 11 workers and 73% showed symptoms. Sauerwald (1961) studied 16 workers and 88% of the subjects showed symptoms and about 80% of the refinery workers showed positive patch tests, but the concentrations of the test solutions (1% sodium hexachloroplatinate(IV) and 0.67% ammonium hexachloroplatinate(IV)) were considered by the author as too high.

However, skin tests were not performed in the latter two studies and no relevant measurements of the platinum content in the air were done.

Parrot *et al.* (1969) conducted a study in France on 51 workers and reported the prevalence of respiratory and/or cutaneous manifestations in 69% of the subjects with symptoms occurring mostly at night and when in the workplace. No skin tests or measurements of the platinum content in the air were conducted.

In a large scale refinery survey published by Murdoch *et al.* (1986), 306 South African platinum refinery workers were investigated. They were accepted for employment on grounds of absence of evidence of atopy. All workers were skin-tested and 12% had a positive skin prick test to platinum halide salts, however, the number of workers with platinum allergy related symptoms or air levels of platinum were not determined.

Venables *et al.* (1989) carried out a historical prospective cohort study in a UK platinum refinery. The study included 91 workers (57 smokers) who commenced work in 1973 and 1974 and was followed up until 1980. Fifty four percent reported respiratory symptoms and 88 workers were skin-tested of which 26% developed a positive skin prick test for platinum salts. Smokers were found to have an increased risk (4-5 times compared to non-smokers) of sensitisation by platinum salts and was the single most important predictor of a positive skin test and of symptoms (the risk was about 2-fold greater). Although it was stated that people with a history of allergy were not employed in the refinery, one third of the workers were considered as atopics. However, the risk from atopy was smaller than that for smoking and was not significant after taking account of smoking.

Baker *et al.* (1990), Biagini *et al.* (1985a) and Brooks *et al.* (1990) conducted a large occupational investigation in the USA. A total of 107 of 123 available current workers and 29 former workers (suspected PSS stated as reason for termination of employment) that reclaimed platinum and other precious metals from scrap metals and consumed catalysts in 1981, were studied. Sixty five percent of the current and 97% of the terminated workers were smokers or ex-smokers. Rhinitis was noted in 44% current and 34% terminated workers, asthma was reported in 29% current and 48%, terminated workers and a positive cold air challenge was found in 11% current and 30% terminated workers. Positive platinum skin prick reaction was obtained in 14% of current and 28% of terminated workers. The reactions in the current workers mostly occurred at concentrations between $10^{-6}$-$10^{-3}$ g/ml, while the terminated workers showed reactions at lower concentrations ($10^{-9}$-$10^{-6}$ g/ml) (Brooks *et al.*, 1990).

Workers in all areas of the facility except the administrative offices showed symptoms of PSS and the sensitivity varied directly with the platinum salt concentrations in the air of the work areas. The risk of demonstrating skin test reactivity to platinum salts was calculated by the authors to increase 13% per 1 μg/m$^3$ increment in the workplace air (Baker *et al.*, 1990). A positive skin prick test was found for 67% of the workers in the tray room (mean air concentration 27.1 μg/m$^3$), for 14% of employees in other areas of the refinery (mean air concentration 10.7 μg/m$^3$) and for 11% of the workers in the analytical laboratories (mean air concentration 0.4 μg/m$^3$. No correlation between air levels and symptoms was presented, but skin test reactivity to platinum salts was significantly correlated with increased prevalences of rhinitis, asthma, reported dermatitis and a positive cold air challenge test, after controlling for aeroallergen sensitivity and cigarette smoking status. A strong association between cigarette smoking and the presence of a positive platinum skin test also was found, but PSS was not found to be associated with atopic tendency. A significant observation was the high prevalence of symptoms consistent with allergic conditions among former workers with a continual positive skin-test although not exposed to platinum salts during an average of five years since termination (Baker *et al.*, 1990). The results of over 75 platinum salt air measurements taken from 1977 to 1979 showed that the levels (geometric means of 8-hour TWA levels) in the refinery, recovery and warehouse areas exceeded 2 μg/m$^3$ and thus the OEL between 50-75% of the time (Baker *et al.*, 1990; Brooks *et al.*, 1990).

Bolm-Audorff *et al.* (1992) studied the prevalence of allergic respiratory tract diseases in 65 employees working at a chemical plant in the platinum-processing departments. The mean duration of platinum exposure was 8.9 years (range 1-40 years). The occurrence of conjunctivitis, rhinitis, coughing, expectoration or dyspnea related to work was reported by 23% of the subjects and these symptoms were found more frequently in the staff with high platinum exposure than in persons with moderate or low exposure. Fifty-two per cent of the workers in the high exposure group suffered from work related symptoms, compared to 14% and 4% of workers in the moderate en low exposure groups, respectively. The group of workers with work-related symptoms showed normal lung function before the beginning of the shift on Monday morning. In the course of the Monday shift and the working week, there was a small but significant fall from 100.7% to 95.9% in forced expiratory volume in one second ($FEV_1$). The forced expiratory flow at 25% of vital capacity ($FEF_{25}$) fell markedly from 95.1% to 73.4%, but the resistance remained unchanged. In the group with symptoms not related to work no significant changes in lung function were found (Bolm-Audorff *et al.*,1992; Lindell, 1997).

Ninety eight percent of workers (n=65) were skin prick tested and a positive cutaneous reaction with potassium hexachloroplatinate(IV) was found in 19% of the employees. A more frequent positive result was obtained in the group with work-related respiratory allergy symptoms (64%) compared to the moderate (20%) and relatively low exposure groups (3%). On the other hand the staff with work-related symptoms showed sensitisation to the general environmental allergens more rarely than did the rest of the staff. The employees had been subdivided into three groups on the basis of the level of platinum exposure (relatively high exposure, moderate exposure, relatively low exposure), but the air levels of platinum for the different groups were not stated. Two stationary air monitorings of platinum salts in the separation shop in 1984 (each over 3.5 hours) revealed an air concentration of <0.2 $\mu g/m^3$ (detection limit) and in 1986 (over 2 hours) showed concentrations of 0.08 and 0.1 $\mu g/m^3$. Two personal air monitorings in filter press workers for 1 hour in 1986 revealed platinum salt concentrations in total dust of <0.05 $\mu g/m^3$ (detection limit). It must be noted that the platinum salt air levels measured during this study never exceeded the German OEL of 2.0 $\mu g/m^3$ and was maintained over the long term (Bolm-Audorff *et al.,* 1992; Lindell, 1997).

Another study conducted by Merget *et al.* (1988, 1991) investigated 24 subjects working in a platinum refinery and 6 former workers (2 workers with recurrent sporadic platinum exposure; four workers with 7, 9, 45 and 96 months since exposure). Eight percent of the current workers and all the former workers suffered from work related symptoms, which include conjunctivitis, rhinitis, asthma and/or cutaneous manifestations (occupational exposure time for the group 8-60 months). Nine refinery workers (occupational exposure time 0.5-306 months) had symptoms that could not be clearly classified as work-related, but one worker from this group developed work-related asthma five months after the study. Twenty of the 24 current worker allowed skin prick test and 20% of these had positive reactions. Smoking was not found to increase the risk of developing PSS, but it was stated that the symptomatic group had a higher exposure to platinum salts than did workers of the other study groups. Platinum salt exposure in the different working areas had been measured by the refinery and was said to be generally below 0.08 $\mu g/m^3$, but no expoure data were presented. Workers with work-related symptoms were considered to have a higher exposure to platinum salts (score points 2.5) compared to workers from the other study groups (score points 1.9 and 1.8), but the exposure level was barely evaluated by the production manager (graded into 1-3 score points) with the drying process of the salts being designated as one of the most dangerous processes (Merget *et al.*, 1988; Lindell, 1997).

Koch and Baum (1996) reported a case of sensitisation in a 36 year old woman with a bridge and crowned teeth consisting of a palladium-platinum alloy. The patient showed recurrent lesions of the oral mucosa, diagnosed as contact stomatitis. Four months after removing the dental palladium- and platinum-containing prostheses, the patient was free of lesions. Patch tests with metal plates and metal salts showed a combined sensitisation to palladium and platinum and histological examination showed an eczematous reaction on the ammonium tetrachloroplatinate(II) test site. Patch testing with small palladium and platinum metal plates showed a local strong positive reaction to palladium and a weak positive reaction to platinum.

Dastychová and Semrádová (2000) reported contact hypersensitivity to soluble platinum salts in a 42-year-old process worker in the manufacture of cisplatin (an inorganic platinum agent: cis-diamminedichloroplatinum with antineoplastic activity) with a widespread papular eczema. The relevant substances tested from his working place namely potassium trichloroammine-platinate(II) and potassium tetrachloroplatinate(II), were found to be positive at day 1 in the patch test (application time: 1 day). The reaction increased with time on the additional reading days 2, 3, and 4.

Newman Taylor *et al.* (1999) investigated the workforce (101 employees) of a large platinum refinery exposed to ammonium hexachloroplatinate(IV) to test the hypothesis that the development of IgE-associated sensitisation to ammonium hexachloroplatinate(IV) was influenced by human leukocyte-associated antigen (HLA) phenotype, especially in those with lower exposure. HLA typing was performed and 44 cases had a positive skin prick test to ammonium hexachloroplatinate(IV) and were compared to 57 nonsensitised referents (matched on age, race, duration of employment, and category of exposure. These results provide evidence that HLA phenotype is a significant determinant of sensitisation to complex platinum salts and for the first time show that the strength of this association varies with intensity of exposure to the sensitising agent. The authors imply that as exposure control measures are taken to prevent occupational sensitisation, disease incidence will increasingly be determined by genetic susceptibility.

Nakayama and Ichikawa (1997) conducted a study at a Japanese factory, where workers are exposed to palladium, platinum, and rhodium (exposure levels unknown) and showed type I (immediate) hypersensitivity symptoms, such as urticaria, bronchial asthma, conjunctivitis, and rhinitis, and at the same time type IV (delayed) hypersensitivity as allergic contact dermatitis.

Twelve of these patients were tested in the following tests: (1) scratch-patch test using Finn Chambers for one hour, (2) conventional closed patch test for two days, and (3) the nasal disc test (only one patient because of severe reactions). In the scratch-patch test, nine patients showed a wheal and flare 20 minutes after application of a single drop of 0.5% aqueous platinum(II) chloride, disappearing a few hours later. In the patch test with 0.5% platinum(II) chloride, eight patients were strongly positive (delayed type contact hypersensitivity: erythema, oedema, and papules on the second and third day). In the nasal test, a single drop of 0.5% platinum(II) chloride on filter paper attached on the nasal mucous membrane instantly produced severe rhinorrhoea, sneezing, wheezing, and an asthma attack (dangerous situation). Every one of the 12 patients tested showed normal values of serum IgE even though the results confirmed the presence of both type I (immediate) and type IV (delayed) hypersensitivity in sensitised workers exposed to platinum(II) chloride.

Santucci ***et al.*** (2000) compared the immunological responses to platinum salts in non-occupationally exposed patients with dermatitis and/or urticaria with occupational exposed workers. In 749 patients with different forms of eczema and 51 subjects with urticaria, the immunological responses to hexachloroplatinic acid, potassium tetrachloroplatinate(II), and sodium hexachloroplatinate(IV) were tested in patch tests ($10^{-2}$ M, 15 μL). All 51 urticaria patients as well as 112 eczematous patients (selected out of the 749 patients on an additional history of respiratory symptoms such as rhinitis, rhinoconjunctivitis, dyspnoea, and asthma) were further tested in prick tests ($10^{-2}$ M). In addition, 153 subjects variably exposed in a plant producing all platinum-group metals (platinum concentrations at the workplace not exactly known; patients were divided in groups of high, medium, and low degree of exposure) were patch ($10^{-2}$ M, 15 μL) and prick ($10^{-8}$-$10^{-2}$ M) tested. In the patch and prick tests, eczematous and urticaria patients never gave positive reactions to the platinum salts. In exposed workers, 1.3% showed a positive patch test reaction to hexachloroplatinic acid at day 2. One of these workers was also positive in the prick test to hexachloroplatinic acid. Another two subjects showed a positive patch test to hexachloroplatinic acid with an urticaria reaction at 25 minutes, however the wheals faded in three hours. Given that platinum-specific antibodies were not identified in these patients, the immunological nature of the contact urticaria was not supported. All four positive workers had clinical symptoms such as rhinitis, asthma, hand dermatitis, and/or urticaria. Positive prick test reactions were found in 14% workers (positive reaction: 9 workers to all three platinum salts, 6 to hexachloroplatinic acid, 4 to hexachloroplatinic acid and potassium tetrachloroplatinate(II), 3 to hexachloroplatinic acid and sodium hexachloroplatinate-(IV). Only 4 workers out of 22 were symptom free.

The clinical manifestations were asthma, rhinitis, and/or urticaria. Results showed that non-occupationally exposed patients tested for platinum salts never showed positive reactions, whereas 22 out of 153 occupationally exposed patients elicited positive reactions. In addition, Santucci *et al.* (2000) reported that environmental platinum did not seem to increase the incidence of reactions to platinum salts in not-occupationally exposed patients with dermatitis and/or urticaria.

Calverley *et al.* (1999) studied 78 healthy recruits accepted for employment in a South African primary platinum refinery during a 24-month prospective study design. Recruits with a history of chronic respiratory disease, allergy symptoms, lung function below prescribed limits or a positive response to skin prick testing with either platinum salts or common allergens were precluded from employment. Subsequently they were categorised as 22 sensitised (positive skin prick test to platinum salts), 46 not sensitised (negative skin prick test and symptom free), and 10 symptomatic subjects not included in either category. During pre-employment 18% of the subsequently sensitised subjects and 17% of the not sensitised subjects was phadiatop positive (presence of inhalant IgE-mediated allergy). Levels of total IgE > 100 kU/L, present in 16 subjects were associated with positive phadiatop status and race. During employment the phadiatop status converted from negative to positive in more sensitised (67%) than unsensitised (16%) subjects. Total IgE levels at outcome had increased in more sensitised subjects, and median levels were higher than in unsensitised subjects. Multivariate analysis showed the likelihood of an increase in total IgE was nine times greater in subjects sensitised to platinum salts, and five times greater with higher platinum salt exposure. Positive responses to skin prick tests with common allergens occurred in 23% sensitised and 24% unsensitised subjects. The results demonstrated that platinum salt sensitivity was not predicted by pre-employment phadiatop or IgE status, but was subsequently associated with conversion to positive phadiatop status, and an increase in total IgE (independent of phadiatop status) (Calverley *et al.*,1999; Health Council of the Netherlands, 2008).

Raulf-Heimsoth *et al.* (2000, 2001) determined the TCR expression, additional cell surface molecules, PBMC, and cytokine production in 17 platinum salt sensitised workers (with workplace related asthma) and 15 asymptomatic non-exposed subjects. All sensitised workers showed a positive immediate-type skin prick test response to sodium hexachloroplatinate(IV), and the IgE concentration was in the range of 17-657 kU/L (median: 110 kU/L). CD3-positive lymphocytes isolated from platinum-sensitised workers showed a significantly higher frequency of Vb-expressing T-cells than controls.

*In vitro*, the hexachloroplatinate(IV) induced lymphocyte proliferation was enhanced in sensitised workers compared to controls and the incidence of enhanced PMBC proliferation was 53% in sensitised workers, and 8.3% in control subjects. Furthermore, a significant increase in CCR3-expressing T-cells and IL-4 and IL-6 production of T-cells (especially from sensitised workers) was noted. *In vitro* stimulation of PBMC from exposed and non-exposed controls with sodium hexachloroplatinate resulted in a time- and dose-dependent increase in specific T-cells. Results showed that a particular TCR repertoire might be a useful biomarker or a possible risk factor for the development of platinum sensitization (Raulf-Heimsoth ***et al.***, 2001).

Linnett and Hughes (1999) presented results of 20 years of medical surveillance at a UK platinum company of all new employees who started work between 1 January 1976 and 31 December 1995. All subjects were medically examined before employment and satisfied standards for work with soluble platinum compounds. Atopic subjects, identified by history or skin prick test to common aeroallergens, were not employed in production or technical positions. The medical surveillance included skin prick tests every 3 months with three different chloroplatinates, spirometry every 6 months and enquiry about symptoms. Smoking habits were recorded before employment. The subjects worked in one of three operations on the same site and were exposed to soluble platinum compounds as chloroplatinates (PGM refinery; n=406), as chloroplatinates with tetraammineplatinum dichloride (TPC lab; n=41) or as tetraammineplatinum dichloride (Autocat; n=100), alone.

Results of personal air sampling for soluble platinum compounds were compared together with the results of medical surveillance. The levels of exposure to soluble platinum compounds in each operation were comparable but the incidence of allergy was significantly different. In a subgroup of workers consistently exposed to chemical processes in each operation, the cumulative chance of being sensitised after 5 years of exposure was estimated as 51% for chloroplatinate exposure, 33% for mixed exposure and 0% for tetraammineplatinum dichloride exposure. The differences in sensitisation rates could neither be explained by age, sex, and atopy, nor by the higher number of smokers in the workers exposed to chloroplatinates, despite the markedly higher risk of sensitisation in smokers. The differences could only be explained by the chemical stability of tetraammine-platinum dichloride (Linnett and Hughes, 1999).

Merget *et al.* (2000; 2001) showed, in a five-year prospective cohort study, a clear dose-response relationship between airborne soluble platinum concentrations, platinum concentrations in sera of exposed workers, and newly occurring sensitisations. The study was conducted from 1989-1995, and included a total of 275 employees working in a catalyst-production plant in Germany. Hundred and fifteen of the employees worked directly in the production lines ("high exposure"), 112 worked regularly or irregularly within the catalyst department but not in the production lines ("low exposure"), and 48 never entered the catalyst building ("no exposure"). Fifty-three per cent of the study population was already present when the study started. The study population consisted of subjects who had undergone at least 2 examinations and a negative response in the skin prick test against platinum at the initial survey. The results demonstrated that in a population of 160 workers, no new cases of sensitisation occurred during 5 year exposure to airborne soluble platinum concentrations in the "no" and "low exposure" areas. The maximum concentrations of soluble platinum measured in the "low exposure" area were 8.6 ng/m$^3$ in 1992 and 1.5 ng/m$^3$ in 1993. In the "high exposure" area, 14 new cases of sensitisation occurred in 115 exposed workers (11%). In this area, the maximum concentrations of soluble platinum measured were approximately 700 ng/m$^3$ in 1992 and 155 ng/m$^3$ in 1993. Personal sampling (of inhalable dust) in this area revealed a median value of 177 ng/m$^3$ with a maximum value of 3700 ng/m$^3$. Although a small fraction (14%) of the samples analysed exceeded the OEL, exposures below the OEL (generally 2000 ng Pt/m$^3$) may still result in sensitisation. Even exposure to soluble platinum salts at levels between 10 and 100 ng Pt/m$^3$ may lead to sensitisation. Smoking cigarettes was positively associated with the occurrence of new symptoms (Health Council of the Netherlands, 2008). Because other sources indicate that sensitisation to platinum salts rarely occurs after 5 years of exposure (Schuppe et al., 1997a) the results of the prospective cohort study of Merget *et al.* (2000, 2001) suggest that exposure levels below 10 ng/m$^3$ would not lead to sensitisation.

*2.13.1.2 Effects of single exposure*

Acute poisoning was reported for a 7-month-old child who died five hours after accidental administration of 8 g of potassium tetrachloroplatinate(II) (Hardman and Wright *et al.*, 1896; Lindell, 1997). A 31-year-old man who ingested 600 mg of potassium tetrachloroplatinate(II), corresponding to around 8 mg/kg body weight (or 4 mg Pt/kg body weight) with an initial serum platinum concentration of 245 µg/dl, suffered from vomiting, diarrhoea, leg cramps, renal failure, gastroenteritis, fever, mild hepatitis, mild metabolic acidosis, eosinophilia and leukocytosis. All symptoms and signs of toxicity disappeared within six days (Woolf and Ebert, 1991; Lindell, 1997).

*2.13.1.3 Effects of repeated exposure*

There are no data regarding other effects than sensitisation and irritation (skin and mucous membranes) in humans repeatedly exposed to soluble platinum salts. Data on the potential health effects in humans following exposure to platinum metal or insoluble salts are absent (Health Council of the Netherlands, 2008).

*2.13.1.4 Genotoxic, carcinogenic, and reproductive and developmental effects*

Data on mutagenicity, carcinogenicity, and reproductive and developmental toxicity in humans following exposure to platinum metal and insoluble or soluble salts have not been reported (Health Council of the Netherlands, 2008).

### 2.13.2 Effects on experimental animals

*2.13.2.1 Irritation and sensitisation*

Animal data (Table 12) indicate that soluble platinum compounds are slightly to severely irritating to the skin, whereas insoluble compounds are not. Further, the soluble compounds are irritating or even severely irritating or corrosive to the eye. No data were found for insoluble compounds (IPCS, 1991). In Table 12, data on skin and eye irritation of several platinum compounds are summarised.

Table 12. Skin and eye irritation by platinum compounds (IPCS, 1991) [a].

| Compound | Water solubility | Skin irritation | Eye irritation |
|---|---|---|---|
| platinum(IV)oxide | insoluble | not irritating [b] | - |
| platinum(II)chloride | insoluble | not irritating [b] | - |
| platinum(IV)chloride | slightly soluble | mildly irritating [b] | - |
| ammonium hexachloroplatinate(IV) | slightly soluble | mildly irritating | - |
| ammonium tetrachloroplatinate(II) | soluble | slightly irritating[c] | corrosive |
| sodium hexachloroplatinate(IV) | very soluble | mildly irritating | irritating |
| sodium hexahydroxyplatinate(IV) | - | severely irritating | - |
| potassium tetrachloroplatinate(II) | soluble | not irritating | irritating |
| potassium tetracyanoplatinate(II) | - | mildly irritanting | irritating[d] |
| tetraammineplatinum dichloride | soluble | moderately irritating | strongly irritating |
| diaminedinitroplatinum(II) | - | not irritating | severely irritating |

a, Tests were carried out according to US Fed. Reg. 1973 guidelines or OECD guidelines; b, Campbell *et al.*, 1975; c, According to HSE, 1996, this compound produced pronounced skin irritation; d, According to HSE, 1996, this compound would currently not be classified as an eye irritant.

Platinum salts may induce bronchoconstriction, anaphylactic shock and elevated plasma histamine levels in animals at the first contact and without any previous exposure to platinum salts, thus through pharmacologic or irritant mechanisms. Increased pulmonary reactivity, expressed as significantly increased pulmonary flow resistance ($R_L$) and decreased forced expiratory volume ($FEV_{0.5}$/FVC), was found in male cynomolgus monkeys (Parrot *et al.*, 1969; Saindelle and Ruff, 1969; Biagini *et al.*, 1983).

Challenged with sodium hexachloro-platinate(IV) aerosols (up to 62.5 mg/mL solutions;) two weeks after a period of repeated inhalation exposure to about 216 μg/m$^3$ of the platinum salt (4 hours/day, biweekly for 12 weeks, particle size: MMAD: 1.61 μm), compared to a challenged, but previously unexposed control group. Increased bronchial reactivity (compared to the control group) was not seen at an exposure level around 1940 μg/m$^3$. However, marked effects on the pulmonary function were found in all exposed and control animals challenged with the platinum salt, and these results indicate a pharmacologic or irritant-mediated bronchoconstriction mechanism for acute exposure to this compound (Biagini *et al.*, 1983; Lindell, 1997).

With the exposure regimens used, no effect on post-exposure baseline pulmonary function was found in exposed animals when challenged with saline. When compared on the basis of monkey-to-human minute volume ratio, a concentration of 200 μg/m$^3$ (4 hours/day, biweekly for 12 weeks) results in an equivalent exposure of three to four times of that to which a worker would be exposed to in one week at an air level of 2 μg/m$^3$ (Biagini *et al.*, 1983; Lindell, 1997).

EPA investigated the potential for skin sensitisation of platinum(IV) chloride and platinum sulphate in rats, mice, and guinea pigs. No allergic induction was shown when 50-350 μg/mL platinum sulphate was repeatedly injected subcutaneously or intravenously, or when platinum sulphate paste (0.1-0.25 g per application) was repeatedly applied to the skin. Also platinum(IV) chloride repeatedly given to guinea pigs (1.5-4.5 mg/mL subcutaneously) was negative when tested for skin reactions 14 days after the last injection (Taubler, 1977).

Ammonium tetrachloroplatinate(II) was tested in the guinea pig maximisation test with Dunkin-Hartley guinea pigs and the local lymph node assay in CBA/Ca mice to predict the skin sensitisation potential. The substance was classified as an extreme sensitiser in the maximisation test (intradermal induction injections: 0.05%; induction patch: 5%; challenge patch: 1%), and was found positive by producing a proliferative response in the lymph node assay (topical applications of 2.5, 5 or 10%) (Basketter and Scholes, 1992).

With respect to mechanisms of action of sensitisation and immune response, a number of studies with soluble platinum compounds have been conducted in mice (Mandervelt *et al.*, 1997; Schuppe *et al.*, 1997a; 1997b; Dearman *et al.*, 1998; Chen *et al.*, 2002).

In summary, studying the immune response in mice using the soluble platinum salts ammonium tetrachloroplatinate(II), sodium hexachloroplatinate(IV), ammonium tetrachloroplatinate(II), ammonium hexachloroplatinate(IV) and/or potassium tetrachloroplatinate(II), the following effects were found (see also Table 7) (Health Council of the Netherlands, 2008):

- stimulation of receptor-mediated endocytosis in Langerhans cells (essential for antigen presentation to pre-T helper cells);
- stimulation of cell proliferation in lymph nodes with the majority of proliferating cells being CD4+ T-cells (T helper cells; essential for cytokine production);
- stimulation of Th2-type cytokine production (IL-4 and IL-10) in lymph node cells (essential for B cell stimulation; stimulation of the humoral immune response);
- inhibition of Th1-type cytokine production (IFN-ɔ) in lymph node cells (essential for macrophage stimulation; suppression of the cell mediated immune response);
- stimulation of anti-nuclear autoantibodies.

The results substantiate the sensitisation potential of soluble platinum salts namely the tetra- and hexachloroplatinates, i.e., salts with a halogen ligand coordinated to platinum. Tetraammine-platinum(II) chloride, where there is no halogen ligand coordinated to platinum but the halogen is present as an ion, failed to induce sensitisation (Health Council of the Netherlands, 2008).

Effects on the mouse immune system are summarised in Table 13 and showed that the differential immunogenicity of the platinum compounds found *in vivo* directly correlated with their capacity to modulate mechanisms of receptor-mediated endocytosis in murine Langerhans cells *in vitro*. Therefore, the *in vitro* endocytosis assay seemed to be useful for predicting the sensitising properties of platinum compounds *in vivo* (Health Council of the Netherlands, 2008).

Table 13. Effects on immunology measured in the mouse (Health Council of the Netherlands, 2008).

| Compound | Species | Assay | Sensitisation | Effects | Reference |
|---|---|---|---|---|---|
| Sodium hexachloroplatinate(IV) $Na_2PtCl_6$ | mouse | LLNA [a], PLN [b], ALN [c] assay | ears (3-4x ec [f]), footpad (1x sc [f]), flank (2x ec) + ears (3x ec) | increased proliferation; increased percentage of CD4+ T-cells enhanced IL-4 and IL-6 levels, decreased IFN-γ, | Mandervelt *et al.*, 1997; Schuppe *et al.*, 1997a; 1997b |
| | mouse | endocytosis assay (Langerhans cells) | - | increased endocytosis | Schuppe *et al.*, 1997a; |
| | mouse | MEST [d] | ear (4-8x ec + challenge(s)) | swelling of the challenged ear (dermal oedema, inflammatory cells); irritant reaction of the contra-lateral ear used for sensitisation | Schuppe *et al.*, 1997b; |
| | mouse | Assay on ANA e | 24x sc | ANA5 production | Chen *et al.*, 2002 |
| Sodium tetrachloroplatinate(II) $Na_2PtCl_4$ | mouse | PLN, ALN assay | footpad (1x sc), flank (2x ec) + ears (3x ec) | increased proliferation; increased percentage of CD4+ T-cells; enhanced IL-4 and IL-6 levels; decreased IFN-γ, | Schuppe *et al.*, 1997a; |
| | mouse | endocytosis assay (Langerhans cells) | - | increased endocytosis | Schuppe *et al.*, 1997a; |
| Potassium tetrachloroplatinate(II) $K_2PtCl_6$ | mouse | PLN assay | footpad (1x sc) | increased proliferation; Increased percentage of CD4+ T-cells | Schuppe *et al.*, 1997a; |
| | mouse | endocytosis assay (Langerhans cells) | - | increased endocytosis | Schuppe *et al.*, 1997a; |
| Tetraammine platinum dichloride $Pt(NH_3)_4Cl_2$ | mouse | PLN assay | footpad (1x sc) | no PLN reaction | Schuppe *et al.*, 1997a; |
| | mouse | endocytosis assay (Langerhans cells) | | no effect | |

a, LLNA: Local Lymph Node Assay, female BALB/c mice (6-week old), n=3/group; b, PLN: Popliteal Lymph Node, female BALB/c mice (8-12-week old), n=5-7/group; c, ALN: Auricular Lymph Node, (1) female BALB/c mice (6-8-week old),n=5/group and (2) female BALB/c mice (8-12-week old), n=5 (test chemicals) and 10 (vehicles)/group; d, MEST: Mouse Ear Swelling Test, female BALB/c mice (6-8 wks old), n=4-5/group; e, ANA: Anti-Nuclear Auto-antibodies, female B10.S mice (4-6 wks old), n=18-20/group; f, ec = epicutaneously; sc = subcutaneously.

### *2.13.2.2 Effects of single exposure*

Within a given class of platinum compounds the acute toxicity follows the water solubility to some degree and generally the insoluble compounds are less toxic than the soluble ones (Holbrook *et al.*, 1975; Holbrook, 1976; IPCS, 1991). Some soluble platinum salts (ammonium tetrachloroplatinate(II), ammonium hexachloroplatinate(IV), potassium tetrachloro-platinate(II), sodium hexachloroplatinate(IV)) are very toxic at peroral administration with $LD_{50}$ values for rats of 25-210 mg/kg bw (around 10-110 mg Pt/kg bw), but many other platinum compounds are moderately or only slightly toxic. $LD_{50}$ values in rat for platinum(IV) oxide and tetraammine-platinum(II) chloride were >3.4 g/kg bw (>2.9 g Pt/kg bw) and >15 g/kg bw (8.8 g Pt/kg bw), respectively, at peroral administration (Holbrook *et al.*, 1975; Holbrook, 1976; IPCS, 1991; Ward *et al.*, 1976). Clinical signs of acute toxicity of ammonium tetrachloroplatinate(II) include diarrhoea, clonic convulsions, laboured respiration, and cyanosis (IPCS, 1991). Hexachloroplatinic acid (40-50 mg/kg intraperitoneally) was highly nephrotoxic (severe tubular necrosis) in rats. Severe histopathological lesions were also observed in thymus (Ward *et al.*, 1976).

Platinum (IV) sulphate administered to mice at the $LD_{25}$ level (213 mg Pt/kg intragastrically) affected their behaviour (general activity) (Lown *et al.*, 1980). Remarkably, pre-treatment of rats with a single lower dose of platinum(IV) chloride 48 hours before a higher generally lethal dose of this salt caused markedly increased survival (Holbrook *et al.*, 1976).

*2.13.2.3 Effects of repeated exposure*

The effects of platinum compounds after repeated exposure have been studied mainly by the use of other routes than inhalation and include decrease in weight gain and effects on kidneys (increased weight and reduced function). There was a decrease in weight gain (and water consumption) in rats given drinking water containing 235 or 470 mg/L (ppm) potassium tetrachloroplatinate(II) for 23 days (Moore *et al.*, 1975b). Transient decrease in weight gain and increased relative kidney weight was seen in male rat at administration of about 40 mg Pt/kg bw/day, when platinum(IV) chloride was added to the drinking water (550 ppm) for four weeks, whereas similar exposure to 10 mg Pt/kg bw/day did not affect body or kidney weights (Holbrook *et al.*, 1975).

The erythrocyte count and hematocrit were reduced by about 13% and a significant increase of creatinine content in plasma, but no influence on body weight gain, was shown in another study in male rat, when platinum(IV) chloride was added in the diet (50 mg Pt/kg diet) for 4 weeks at doses equivalent to approximately 5 mg Pt/kg bw/day (Reichlmayr-Lais *et al.*, 1992). In a similar experiment with platinum(II) chloride, neither hematological parameters, plasma creatinine nor body weight gain were affected (Reichlmayr-Lais *et al.*, 1992).

No treatment-related changes in haematological values, growth rate or kidney weights were noticed when female rats were fed a diet containing platinum(IV) chloride in a concentration of up to 100 mg Pt/kg diet, four weeks before and during gestation (Bogenrieder *et al.*, 1992). Data on inhalation exposure are very limited and unreliable. No evident ill effects and no significant differences in body weights were observed for male Cynomolgus monkeys exposed by inhalation to 177 $\mu g/m^3$ ammonium hexachloroplatinate(IV) for 12 weeks (6 hours/day, 5 days/ week; MMAD 1 $\mu m$). However, the study was designed to detect differences in immunologic parameters and effects in the airways (Biagini *et al.*, 1986).

*2.13.2.4 Genotoxicity and cytotoxicity*

For the only insoluble platinum compound tested, namely platinum(II)chloride, *in vitro* tests for mutations (mouse lymphoma L5178Y cells) (Sandhu, 1979) and DNA damage in bacteria (*E.coli*: SOS chromotest) (Gebel *et al.*, 1997) and mammalian cells (human lymphocytes: comet assay) (Migliore *et al.*, 2002) were negative. Both positive (Migliore *et al.*, 2002) and negative Gebel *et al.*, 1997) results were reported in micronucleus tests in human lymphocytes. The induction of micronuclei was due both to clastogenic and aneuploidogenic mechanisms (Migliore *et al.*, 2002).

Numerous soluble platinum compounds have been tested for their mutagenic activity *in vitro* in bacterial and mammalian cell systems, mostly without metabolic activation, and in fruit flies. Many of the compounds were positive. Some of the compounds were tested for other end points in other systems (e.g. *E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes/leukocytes: micronucleus test and comet assay), inducing both positive and negative results (Uno and Morita, 1993; Bünger *et al.*, 1996, 1997; HSE,1996; Gebel *et al.*, 1997; Migliore *et al.*, 2002).

The anti-neoplastic agent cisplatin binds to DNA and is mutagenic *in vitro* and *in vivo*. Platinum compounds with a similar structure and configuration, particularly complexes with the same square-planar configuration of cis-$PtN_2X_2$, generally also have mutagenic activity (Uno and Morita, 1993). The results of genotoxicity studies are summarised in Table 14.

Table 14. Genotoxic activity of some platinum salts in different test systems (Health Council of the Netherlands, 2008).

| Compound | Test system | Metabolic activation | Result | Reference |
|---|---|---|---|---|
| Platinum(II) chloride | *E. coli* PQ37; SOS chromotest | - | - | Gebel *et al.*, 1997 |
| | mouse lymphoma L5178Y cells; mutation assay | - | - | Sandhu,1979; |
| | human lymphocytes; micronucleus test | - | - | Gebel *et al.*, 1997 |
| | human lymphocytes; micronucleus test + FISH [a] | - | + | Migliore *et al.*, 2002 |
| | human leukocytes; comet assay | - | - | Migliore *et al.*, 2002 |
| Platinum(IV) chloride | *S. typhimurium* TA98; mutation assay | - | + | Kanematsu *et al.*, 1980 |
| | *S. typhimurium* TA100, TA1535, TA1537, TA1538; mutation assay | - | - | Kanematsu *et al.*, 1980, Uno and Morita, 1993 |
| | *E. coli* B/r WP2 *try*, WP2 *hcr try*; mutation assay | - | - | Kanematsu *et al.*, 1980 |
| | *E. coli* PQ37 ; SOS chromotest | - | + | Gebel *et al.*, 1997 |
| | *B. subtilis* H17 M45 ; rec-assay | - | + | Kanematsu *et al.*, 1980 |
| | *D. melanogaster*; sex-linked recessive lethal mutation assay | | + | Woodruff *et al.*, 1980 |
| | Chinese hamster lung V79 cells; mutation assay | - | + | Kanematsu *et al.*, 1990 |
| | Chinese hamster ovary S cells; mutation assay | - | + | Taylor *et al.*, 1979b |
| | Chinese hamster ovary AUXB1 cells; mutation assay | - | + | Taylor *et al.*, 1979b |
| | mouse lymphoma L5178Y cells ; mutation assay | - | + | Sandhu,1979; |
| | human lymphocytes; micronucleus test | - | + | Gebel *et al.*, 1997 |
| | human lymphocytes; micronucleus test + FISH [a] | - | + | Migliore *et al.*, 2002 |
| | human leukocytes; comet assay | - | + | Migliore *et al.*, 2002 |
| | Syrian hamster embryo cells; cell transformation assay | - | + | Casto *et al.*, 1979 |
| Platinum(IV) sulphate | Chinese hamster ovary S cells; mutation assay | - | + | Smith *et al.*, 1984; Taylor *et al.* 1979a |
| | Chinese hamster ovary AUXB1 cells; mutation assay | - | + | Taylor *et al.*, 1985 |
| Hexachloroplatinic (IV) acid | *S. typhimurium* TA98; mutation assay | + | + | Uno and Morita, 1993 |
| | *S. typhimurium* TA 100; mutation assay | + | - | Uno and Morita, 1993 |
| | *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 ; mutation assay | - | - | Kanematsu *et al.*, 1980 |
| | *E. coli* B/r WP2 *try*, WP2 *hcr try*; mutation assay | - | - | Kanematsu et al., 1980 |
| | *B. subtilis* H17 M45 ; rec-assay | - | + | Kanematsu et al., 1980 |
| Potassium tetra-chloroplatinate(II) | *S. typhimurium* TA98, TA100; mutation assay | -/+ | +/+ | Lecointe *et al.*, 1977; Uno and Morita, 1993 |
| | *E. coli* PQ37; SOS chromotest | - | + | Gebel *et al.*, 1997 |
| | *S. cerevisiae* ; assay for aneuploidy | - | + | Sora *et al.*, 1988 |
| | *D. melanogaster*; sex-linked recessive lethal mutation assay | | - | HSE, 1996 |
| | Chinese hamster ovary S cells; mutation assay | - | - | Taylor *et al.*, 1979a |
| | Chinese hamster ovary AUXB1 cells; mutation assay | - | + | Taylor *et al.*, 1978 |
| | Chinese hamster ovary K1-BH4 cells; mutation assay | - | (+) [b] | Hsie, 1981; Johnson *et al.*, 1980 |
| | Human blood lymphocytes; micronucleus test | - | + | Gebel et al., 1997 |
| Potassium hexa-chloroplatinate(IV) | *S. typhimurium* TA97a, TA98, TA100, TA102 ;mutation assay | -/+ | +/+ | Bünger *et al.*, 1996; 1997 |
| | *E. coli* PQ37 ; SOS chromotest | - | - | Gebel *et al.*, 1997 |
| | Chinese hamster ovary S cells; mutation assay | - | + | Smith *et al.*, 1984; Taylor *et al.*, 1979a |
| | Chinese hamster ovary AUXB1 cells; mutation assay | - | + | Taylor *et al.*, 1978 |
| | human lymphocytes; micronucleus test | - | - | Gebel *et al.*, 1997 |
| Ammonium hexa-chloroplatinate(IV) | *S. typhimurium* TA97a, TA98, TA100, TA102 ;mutation assay | -/+ | +/+ | Bünger *et al.*, 1996; 1997 |
| | *S. typhimurium* TA98, mutation assay | - | + | Kanematsu *et al.*, 1980 |
| | *S. typhimurium* TA1537,TA1538, mutation assay | - | - | Kanematsu *et al.*, 1980 |
| | *E. coli* B/r WP2 try; mutation assay | - | - | Kanematsu *et al.*, 1980 |
| | *E. coli* WP2 hcr try; mutation assay | - | + | Kanematsu *et al.*, 1980 |
| | *B. subtililis* H17 M45 ; rec-assay | - | + | Kanematsu *et al.*, 1980 |
| Ammonium tetra-chloroplatinate(II) | *S. typhimurium* TA97a, TA98, TA100, TA102; mutation assay | -/+ | +/+ | Bünger *et al.*, 1996; 1997 |
| | Human lymphocytes; micronucleus test + FISH a | - | + | Migliore *et al.*, 2002 |
| | Human leukocytes; comet assay | - | - | Migliore *et al.*, 2002 |
| Tetraammine-platinum dichloride | S. typhimurium TA98, TA100 ; mutation assay | -/+ | -/- | Uno and Morita, 1993 |
| | S. typhimurium TA100; mutation assay | not given | + | Lecointe *et al.*, 1977 |
| | S. typhimurium TA98, TA100, TA1535, TA1538; mutation assay | not given | - | HSE, 1996 |
| | S. typhimurium TA1537; mutation assay | -/+ | +/+ | HSE, 1996 |
| | Chinese hamster ovary K1-BH4 cells; mutation assay | - | - | Hsie, 1981; |
| | D. melanogaster; sex-linked recessive lethal mutation assay | | - | Johnson *et al.*, 1980 HSE, 1996 |

a, FISH = fluorescence *in situ* hybridisation; this technique enables to ascribe micronucleus induction to clastogenic oraneuploidogenic mechanisms; b, Marginallyôpositive.

An *in vitro* study on cytotoxicity was reported by Mazzotti *et al.* (2002). They reported dose-effect curves and $EC_{50}$ (50% inhibition of cell growth) values of ammonium hexachloro-platinate(IV) and ammonium tetrachloroplatinate(II) measured in the second phase of a programme. This included a systematic *in vitro* study on the carcinogenic potential of metal compounds with Balb/3T3 clone A31-1-1 mouse fibroblasts (Balb/3T3 cell transformation assay). Ammonium hexachloroplatinate(IV) and ammonium tetrachloroplatinate(II) were tested in the range of 0.1-100 µM by incubating attached Balb/3T3 cells for 72 hours. After exposure, the metal solution was substituted with non-treated culture medium. Seven days later, colonies containing Ó50 cells were scored, and the relative colony-forming efficiency (CFE) was expressed as a percentage of those observed in untreated control cultures. Both compounds showed a clear dose-response effect. From the dose response curves, the $EC_{50}$ values were calculated to be 0.0037 mM for ammonium hexachloroplatinate(IV) and 0.055 mM for ammonium tetrachloroplatinate(II) (Table 15). These results indicate that the cytotoxicity of platinum compounds is influenced by the chemical nature of the platinum compounds (Health Council of the Netherlands, 2008).

Table 15. Cytotoxicity of some soluble platinum salts (Health Council of the Netherlands, 2008).

| Compound | Indicator cell | $EC_{50}$ [a] (mM) | Reference |
|---|---|---|---|
| Ammonium hexa-chloroplatinate(IV) | L929, mouse fibroblasts cell line | 0.4 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |
| | L132, human embryonic lung cell line | 0.4 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |
| | Balb/3T3, mouse fibroblasts | 0.0037 | Mandervelt *et al.*, 1997 |
| Ammonium tetra-chloroplatinate(II) | L929, mouse fibroblast cell line | 0.3 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |
| | L132, human embryonic lung cell line | 0.8 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |
| | Balb/3T3, mouse fibroblasts | 0.055 | Mandervelt *et al.*, 1997 |
| Potassium hexa-chloroplatinate(IV) | L929, mouse fibroblasts cell line | 0.2 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |
| | L132, human embryonic lung cell line | 0.6 | Calverley *et al.*, 1999; Raulf-Heimsoth *et al.*, 2001 |

a, EC50 = concentration at which 50% reduction of cell viability or 50% inhibition of cell growth was observed,respectively.

### *2.13.2.5 Carcinogenicity*

Studies on the potential carcinogenicity of platinum metal and platinum compounds were not located except for cisplatin and some related compounds which are known carcinogens (Health Council of the Netherlands, 2008)

### *2.13.2.6 Reproductive and developmental toxicity*

Data on reproductive and developmental toxicity are very limited and are summarised in Table 16. No effects were seen in rat foetuses (weight, resorptions, malformations) following daily administration of doses of platinum metal or platinum(IV) chloride of 0.1-100 mg Pt/kg diet, for 4 weeks before pregnancy to gestational day 20 (Bogenrieder *et al.*, 1992 cited in Health Council of the Netherlands, 2008).

Further, no effects on weight or haematology were seen in the offspring, when platinum(II) chloride or platinum(IV)chloride (up to 100 mg Pt/kg diet) was given in the diet of lactating rats for 21 days (Reichlmayr-Lais *et al.*, 1992).

In contrast, single oral (gavage) doses of platinum(IV) sulphate (200 mg Pt/kg bw) caused a reduction of pup weights when administered to female Swiss ICR mice at gestational day 7 or 12, and a decreased activity when administered at lactational day 2. Single subcutaneous treatment with sodium hexachloro-platinate(IV) (20 mg Pt/kg bw) only resulted in decreased pup activity when administered on gestational day 12 (DôAgostino *et al.*, 1984). Platinum(IV)chloride (total dose: 16 mg Pt/kg bw) administered subcutaneously for 30 days to male Swiss mice or intratesticularly once to male albino rats resulted in largely decreased testis weights in both species and in spermatogenic arrest in mice and total testicular necrosis and destruction of all spermatozoa in rats (Kamboj and Kar, 1964).

Table 16. *In vivo* effects on reproduction and development (Health Council of the Netherlands, 2008).

| Compound | Species | Exposure | Effects | Reference |
|---|---|---|---|---|
| Platinum | rat (female; Sprague-Dawley) | 0.1-100 mg Pt/kg diet/day from 4 weeks before pregnancy till gestational day 20 | no effects on fetuses (weight, resorptions, malformations) | Bogenrieder *et al.*, 1992 |
| Platinum(II) chloride | rat (female; Sprague-Dawley) | 0.1-100 mg Pt/kg diet/day during lactation | no effect on offspring (weight; haematology) | Reichlmayr-Lais *et al.*, 1992 |
| Platinum(IV) chloride | rat (female; Sprague-Dawley) | 0.1-100 mg Pt/kg diet/day from 4 weeks before pregnancy till gestational day 20 | no effects on fetuses (weight, resorptions, malformations) | Bogenrieder *et al.*, 1992 Reichlmayr-Lais *et al.*, 1992 |
| | | during lactation | no effect on offspring (weight; haematology) | |
| | rat (male; albino) | 16 mg Pt/kg bw, intratesticular; single dose | largely decreased testis weights; total testicular necrosis and destruction of all spermatozoa | Kamboj and Kar, 1964 |
| | mouse (male; Swiss) | 0.5 mg Pt/kg bw/day, subcutaneous; for 30 days | largely decreased testis weights; spermatogenic arrest | Kamboj and Kar, 1964 |
| Platinum sulphate | mouse (female; Swiss ICR) | 200 mg Pt/kg bw, gavage; single dose gestational day 7 or 12 | reduced offspring weight | DôAgostino *et al.*, 1984 |
| | | post-natal day 2 | decreased activity | |
| Sodium hexa-chloroplatinate(IV) | mouse (female; Swiss ICR) | 20 mg Pt/kg bw, subcutaneous; single dose gestational day 7 or 12 | reduced offspring weight (only at day 12) | DôAgostino *et al.*, 1984 |
| | | lactational day 2 | no effect | |

*In vitro* experiments (human sperm cells; Sprague-Dawley rat Sertoli cells) (Holland and White 1980; Holt, 1987) indicate that soluble platinum compounds may influence sperm function by induction of spermatogenic arrest and the acrosome reaction, reduction of the sperm motility, and effects on Sertoli cells (indirect effect). The *in vitro* effects on reproduction are summarised in Table 17.

Table 17. *In vitro* effects on reproduction (Health Council of the Netherlands, 2008).

| Compound | Species/cell types | Exposure | Effects | Reference |
|---|---|---|---|---|
| Hexachloroplatinic acid | Rat[a] Sertoli cells | 5-100 μM, 24 h | increased mitrochondrial dehydrogenase activity and lactate production; Ü-inhibin production: at 5-10 μM Pt: increased at >20 μM Pt: decreased | Holt, 1987 |
| Sodium hexachloroplatinate(IV) | Human[b] spermatozoa | 0.5-1000 μM | induction of the acrosome reaction (independent on $Ca^{2+}$; dependent on protein kinase A or C); reduced sperm motility | Hostynek *et al.*, 1993 |
| tetraamminedichloroplatinum(II) | Human[b] spermatozoa | 0.5-1000 μM | induction of the acrosome reaction (independent on $Ca^{2+}$; dependent on protein kinase A or C); reduced sperm motility | Hostynek *et al.*, 1993 |

a, Sprague-Dawley rats (18-day old), number not given; b, Healthy donors with normal sperm parameters according to WHO, 1992.

## 2.14 EXISTING GUIDELINES, STANDARDS AND EVALUATIONS

### 2.14.1 Existing guidelines and standards

The Regional Office for Europe of the World Health Organisation did not recommend a specific air quality guideline for platinum for the general population (WHO, 2000). OELs for platinum and platinum compounds for the working population obtained from the most recent publications are listed in Table 18.

Table 18. Occupational exposure limits for platinum and platinum compounds

| Country - organisation | OEL ($mg/m^3$) | | TWA | Type of OEL | Note[a] | Reference[b] |
|---|---|---|---|---|---|---|
| | Pt metal | Soluble Pt salts (as Pt) | | | | |
| The Netherlands | | | | | | |
| - Ministry of Social Affairs and Employment | 1 | | 8 h | Legally binding | - | HSE, 1985 |
| Germany | | | | | | |
| - DFG MAK-Commission | - | -[c] | | | sens[d] | HSE, 1996 |
| - AGS | - | - | | | | Hsie, 1981 |
| Norway | - | 0.002 | 8 h | | | Hughes; 1980 |
| Sweden | 1[e,f] | 0.002[f] | 8 h | | sens[g] | Hunter *et al.*,1945 |
| Denmark | 1 | 0.002 | 8 h | | | Hägg, 1963 |
| Finland | 1 | 0.002 | 8 h | | | IARC 1981 |
| Iceland | 1 | 0.002 | 8 h | | | IARC 1981 |
| United Kingdom | | | | | | |
| - HSE | 5 | 0.002 | 8 h | WEL | | IPCS, 1991 |
| USA | | | | | | |
| - ACGIH | 1 | 0.002 | 8 h | TLV | | Jacobs, 1987 |
| - OSHA | - | 0.002 | 8 h | PEL | 65 | Johnson *et al.*, 1976 |
| - NIOSH | 1 | 0.002 | 10 h | REL | | Johnson *et al.*, 1976 |
| South Africa | | | | | | |
| - MHSA | 5 | 0.002 | 8h | TWA | sens | MHSA, 1996 |
| European Union | | | | | | |
| - SCOEL | 1 | - | | IOELV | 66 | Johnson *et al.*, 1975 |

a, S = skin notation; which means that skin absorption may contribute considerably to body burden; sens =substance can cause sensitisation; b, Reference to the most recent official publication of OELs; c, Listed among substances for which no MAK value could be established because studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values. However, it is noted that a peak value of 0.002 $mg/m^3$ for platinum compounds (chloroplatinates) should not be exceeded; d, Danger of sensitisation of both airways and skin; e, Holds also for poorly soluble platinum compounds; f, Total dust; g, Soluble platinum compounds; h, Certain chloroplatinates excepted.

### 2.14.2 Previous evaluations by national and international bodies

*2.14.2.1 Health and Safety Executive*

Recently the UK HSE has published a criteria document on platinum metal and its salts and concluded that exposure to the chlorinated platinum salts (soluble) leads to skin and respiratory hypersensitivity in humans, but stated that the available data do not allow conclusions to be drawn as to whether or not a threshold for respiratory sensitisation exists. In addition, HSE stated that it is unlikely that platinum metal will give rise to the effects as seen for the soluble chlorinated platinum salts. It recommended to retain the occupational exposure standard (OES; 8-hour TWA) of 5 mg/m$^3$ for platinum metal and insoluble platinum salts, and recommended a maximum exposure limit (MEL) of 2 μg/m$^3$ for soluble platinum salts (HSE, 1996)

*2.14.2.2 The American Conference of Governmental Industrial Hygienists*

ACGIH concluded in the documentation of the TLV(s) of platinum and soluble compounds, that occupational exposures to soluble complex salts of platinum, but not elemental platinum, had caused progressive allergic reactions that led to pronounced asthmatic symptoms and that skin sensitisation had also occurred. The limited air sampling data indicated the need to maintain the concentration of airborne soluble platinum salts at a very low level to protect employees against the potential development of respiratory irritation, respiratory allergy, and dermatitis. ACGIH recommended, therefore, a TLV-TWA of 0.002 mg/m$^3$ for soluble salts, measured as platinum, to minimise the potential for platinum salt-induced asthma and sensitisation. For platinum metal dust, ACGIH recommended a TLV-TWA of 1.0 mg/m$^3$ because this exposure has not been associated with the development of allergic or other diseases (Johnson ***et al.***, 1975).

*2.14.2.3 World Health Organization*

The International Programme on Chemical Safety (IPCS/WHO) published an Environmental Health Criteria document on platinum and platinum compounds and concluded that: (1) the most significant health effect from exposure to soluble platinum salts is sensitisation, and that some (soluble) halogenated platinum salts are highly allergenic in humans, (2) that there is no evidence for sensitisation from platinum metal, (3) that the present occupational exposure limit of 2 μg/m$^3$ might not be adequate to prevent (soluble) platinum-salt hypersensitisation, and that workplace exposure should be as low as practicable to minimise the risk. In addition, it was stated that data assessing the carcinogenic risk platinum pose to humans are lacking (IPCS, 1991).

*2.14.2.4 WHO: Regional Office for Europe*

In the second edition of the Air Quality Guidelines, it was concluded that sensitisation reactions in occupational settings have been observed down to the limit of detection of 0.05 μg/m$^3$, for soluble platinum but that these effects were limited to individuals previously sensitised by higher exposure levels. WHO stated that it is unlikely that the general population exposed to ambient concentrations of soluble platinum, which are at least three orders of magnitude lower, will develop similar effects. Therefore, no specific limit was recommended, but further studies were suggested, in particular on the speciation of platinum in the environment (Johnson ***et al***., 1980)

*2.14.2.5 Health Based recommended occupational exposure limit*

The Dutch Expert Committee on Occupational Standards (DECOS) recommends a health-based OEL for chloroplatinates of 5 ng/m$^3$ (as Pt), as an 8-hour TWA concentration as inhalable dust. For platinum metal, insoluble platinum compounds, and soluble compounds other than chloroplatinates, no health-based occupational exposure limits can be recommended. In addition DECOS concluded that the toxicological database does not allow the recommendation of a health-based OEL for soluble platinum compounds. However, the committee believes the data reported by Linnett and Hughes (1999) indicate that an OEL of 0.5 μg/m$^3$ for tetraamminedichloroplatinum(II) is not associated with toxicity, and might be used as an upper limit for workers (Health Council of the Netherlands).

## 2.15 RECOMMENDATIONS FOR RESEARCH

Due to analytical problems and difficulties in establishing platinum reference values in blood and urine no method can until now be applied for the effective monitoring of platinum. The absence of adequate reference values makes it difficult to establish relationships (dose-effect relationship) between platinum concentrations, toxic effects and air levels. Most available analytical methods are not sensitive enough to monitor low levels of platinum in occupationally exposed workers and although adsorptive voltammetry is extremely sensitive, it must be further assessed before it can be effectively utilised in practice (Lindell, 1997). In addition, current analytical methods do not distinguish between halogeno-platinates and other soluble platinum compounds. Consequently new analytical methods are required to establish the speciation of platinum in the environment given that not all platinum species elicit sensitisation. Data on reproduction toxicology, genotoxicity, and carcinogenicity is very limited. The antineoplastic agent cisplatin and some analogues bind to DNA and are mutagenic and have shown to be carcinogenic in animal studies.

The mutagenicity and carcinogenicity of other platinum compounds is less well investigated although differences in chemical reactivity (lability of ligands, number of active sites etc) give reason to expect that not all forms of platinum pose PSS. However, many platinum salts and complexes have been shown to be mutagenic *in vitro* and consequently further research e.g. animal studies, cytogenetic tests and well performed epidemiological studies are necessary to get a better insight into the toxicological outline of platinum and its water-soluble and insoluble salts (Lindell, 1997; Health Council of the Netherlands, 2008).

## 2.16 SUMMARY

Human and experimental animal data available indicate that halogenated platinum salts (charged compounds with reactive ligands) provoke sensitising and allergic reactions of the respiratory tract and skin, whereas uncharged complexes and non-halogenated platinum salts have been shown to be non-allergenic (IPCS, 1991; WHO 2000). The mechanism of platinum salt allergy is likely to be a type I, IgE-mediated response with platinum salts of low relative molecular mass, acting as haptens which combine with serum proteins to form the complete antigen. Smokers seem to be more susceptible to the sensitising effects of platinum salts compared with healthy non-smoking subjects. Furthermore, once sensitisation has developed, subsequent exposure to minute concentrations of platinum salts have elicited both immediate and late-onset reactions and it is not possible to define a no-effect level for these platinum compounds (Lindell,1997).

In occupational settings, elicitation of allergic symptoms occurs at platinum air levels below 2 $\mu g/m^3$ and sensitisation have been observed down to the limit of detection of 0.05 $\mu g/m^3$. There is no convincing evidence for sensitisation or for other adverse health effects following exposure to platinum metal (metallic platinum) and no reports of other effects of platinum compounds than allergy/irritation at occupational exposure (WHO, 2000).

Because the correlation between platinum exposure concentration and the development of sensitisation is unknown, the WHO Task Group concluded that a proposed reduction in the OEL cannot be justified. The Task Group did, however, recommend that the OEL of 2 $\mu g/m^3$ be changed from an 8-hour TWA to a ceiling value, and that personal sampling devices be used in conjunction with area sampling to determine more accurately the exact platinum exposure. Should it be established that sensitisation has occurred consistently at levels below the OEL and that intermittent, short exposures above this level had not taken place, there would be strong grounds for reducing the OEL (WHO, 2000).

Many platinum salts/complexes are mutagenic *in vitro*, but it is not possible from the available studies to draw conclusions regarding the genotoxic risk in the work environment. There are no experimental data regarding the carcinogenic activity of platinum and its compounds with the exception of *cis*-platin, for which there is sufficient evidence for carcinogenic activity in animals and was classified by IARC as a group 2A carcinogen (sufficient evidence for carcinogenicity in animals but inadequate evidence in humans). There are no data available to assess the carcinogenic risk of platinum or its compounds in humans, and no recent epidemiological studies of cancer incidence or mortality in platinum workers have been reported (Lindell, 1997; WHO, 2000).

## 2.17 REFERENCES

1. Acts see South Africa.

2. Alt F, Messerschmidt J. (1993) Edelmetallemissionen durch Katalysatoren-Beitrag der Analytischen Chemie zur Abschätzung des Gefahrenpotentials. In: Dörner K, ed. Akute und chronische Toxizität von Spurenelementen, Stuttgart: Wissenschaftliche Verlagsgesellschaft: 85-92. (Cited in the Health Council of the Netherlands, 2008).

3. American Conference of Industrial Hygienists (ACGIH). (1990) Threshold limit values for chemical substances and physical agents and biological exposure indices for 1990-1991. Cincinnati, OH, American Conference of Governmental Industrial Hygienists.

4. Artelt S, Kock H, König HP, Levsen K, Rosner G. (1999a) Engine dynamometer experiments: platinum emissions from differently aged three-way catalytic converters. Atmos Environ; 33(21): 3559-3567.

5. Artelt S, Creutzenberg O, Kock H, Levsen K, Nachtigall D, Heinrich U, Rühle T, Schlögl R. (1999b) Bioavailability of fine dispersed platinum as emitted from automotive catalytic converters: a model study. Sci Total Environ; 228(2-3): 219-242.

6. Bader R, Reichlmayr-Lais AM, Kirchgessner M. (1992) Effekte von alimentärem metallischen Platinbei wachsenden Ratten in Abhängigkeit von der Applikationsdauer und der Partikelgrösse. J Anim Physiol Anim Nutr; 67: 181-187. (Cited in the Health Council of the Netherlands, 2008).

7. Baker DB, Gann PH, Brooks SM, Gallagher J, Bernstein IL. (1990) Cross-sectional study of platinum salts sensitization among precious metals refinery workers. Am J Ind Med; 18: 653-664.

8. Basketter DA, Scholes EW (1992) Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens. Food Chem Toxic; 30: 65-69.

9. Baumgärtner ME, Raub CJ. (1988) The electrodeposition of platinum and platinum alloys. Platinum Metals Rev; 32: 188-197.

10. Beliles RP. (1994) Platinum-group metals: platinum, Pt; palladium, Pd; iridium, Ir; osmium, Os; rhodium Rh; ruthenium Ru. In: Clayton GD, Clayton FE, eds. Pattyôs Industrial Hygiene and Toxicology; 4th ed 2C: 2183-2201. New York: John Wiley and Sons. ISBN 0471547263.

11. Benes B, Jakubec K, Smid J, Spevackova V. (2000) Determination of thirty-two elements in human autopsy tissue. Biol Trace Elem Res; 75(1-3): 195-203.

12. Bernstein IL, Brooks SM. (1993) Metals. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. Asthma in the Workplace. New York: Marcel Dekker, 459-479.

13. Biagini RE, Moorman WJ, Smith RJ, Lewis TR. (1983) Pulmonary hyperreactivity in cynomolgus monkeys (macaca fasicularis) from nose-only inhalation exposure to disodium hexachloroplatinate, $Na_2PtCl_6$. Toxicol Appl Pharmacol; 69: 377-384.

14. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. (1985a) The diversity of reaginic immune responses to platinum and palladium metallic salts. J Allergy Clin Immunol; 76: 794-802.

15. Biagini RE, Moorman WJ, Lewis TR, Bernstein IL. (1985b) Pulmonary responsiveness to methacholine and disodium hexachloroplatinate ($Na_2PtCl_6$) aerosols in cynomolgus monkeys (macaca fascicularis). Toxicol Appl Pharmacol; 78: 139-146.

16. Biagini RE, Moorman WJ, Lewis TR, Bernstein IL. (1986) Ozone enhancement of platinum asthma in a primate model. Am Rev Respir Dis; 134: 719ï 725.

17. Bogenrieder A, Reichlmayr-Lais AM, Kirchgessner M. (1992) Einfluss von alimentärem $PtC_{l4}$ und $Pt^0$ auf Wachstum, hämatologische Parameter und auf Reproduktionsleistung. J Anim Physiol Anim Nutr; 68: 281-288. (Cited in the Health Council of the Netherlands, 2008).

18. Boggs PB. (1985) Platinum allergy. Cutis; 35: 318-320.

19. Bolm-Audorff U, Bienfait HG, Burkhard J, Bury AH, Merget R, Pressel G, Schultze-Werninghaus G. (1992) Prevalence of respiratory allergy in a platinum refinery. Int Arch Occup Environ Health; 64: 257-260.

20. Boshoff JCJ. (2000) A general overview of platinum tailings disposal in South Africa. Mining World: 18, Augustus.

21. Bradford CW. (1988) Platinum. In: Seiler HG, Sigel H, eds. Handbook on Toxicity of Inorganic Compounds: 533-539. New York: Marcel Dekker.

22. Brooks SM, Baker DB, Gann PH, Jarabek AM, Hertzberg V, Gallagher J, Biagini RE, Bernstein IL. (1990) Cold air challenge and platinum skin reactivity in platinum refinery workers. Chest; 97: 1401-1407.

23. Bünger J, Stork J, Stalder K (1996) Cyto- and genotoxic effects of coordination complexes of platinum, palladium and rhodium in vitro. Int Arch Occup Environ Health; 69(1): 33-38.

24. Bünger J (1997) Automobile exhaust catalyst from the viewpoint of environmental and occupational medicine. Part 2: cytotoxicity and mutagenicity of metals belonging to the platinum group. Zentralblatt Arbeitsmedizin Arbeitsschutz Ergon; 47(2): 56-60.

25. Bullock J. (2010) Chloroplatinate Toxicity: Use and Misunderstanding of Merget. International Precious Metals Institute. USA: Tucson, Arizona.

26. Calverley AE, Rees, D, Dowdeswell RJ, Linnett PJ, Kielkowski D. (1995) Platinum salt sensitivity in refinery workers: incidence and effects of smoking and exposure. Occup Environ Med; 52: 661ï 666.

27. Calverley AE, Rees D, Dowdeswell RJ. (1999) Allergy to complex salts of platinum in refinery workers: prospective evaluations of IgE and Phadiatop status. Clin Exp Allergy; 29(5): 703-711.

28. Calverley AJ, Murray J. (2005) South Africa's mines: treasure chest or Pandora's box? S Afr J Sci; 101(3): 109-112.

29. Casto BC, Meyers J, DiPaolo JA (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res; 39: 193-198.

30. Chen M, Hemmerich P, von Mikecz A (2002) Platinum-induced autoantibodies target nucleoplasmic antigens related to active transcription. Immunobiol; 206(5): 474-483.

31. Cleare MJ, Hughes EG, Jacoby B, Pepys J. (1976) Immediate (type I) allergic responses to platinum compounds. Clin Allergy; 6: 183-195.

32. Comité Européen de Normalization (CEN). (1995) Workplace atmospheres: pumps for personal sampling of chemical agents - requirements and test methods prEN 1232 CEN. BS EN 1232. ISBN 0580283283.

33. Cromwell O, Pepys J, Parish WE, Hughes EG. (1979) Specific IgE antibodies to platinum salts in sensitized workers. Clin Allergy; 9: 109-117.

34. D´Agostino RB, Lown BA, Morganti JB, Chapin E, Massaro EJ. (1984) Effects on the development of offspring of female mice exposed to platinum sulfate or sodium hexachloroplatinate during pregnancy or lactation. J Toxicol Environ Health; 13: 879-891.

35. Dally MB, Hunter JV, Hughes EG, Stewart M, Newman-Taylor AJ. (1980) Hypersensitivity to platinum salts: a population study. Am Rev Respir Dis; 121, Suppl. 230.

36. Dastychová E, Semrádová V. (2000) A case of contact hypersensitivity to platinum salts. Contact Dermatitis; 43(4): 226.

37. Dearman RJ, Basketter DA, Kimber I (1998) Selective induction of type 2 cytokines following topical exposure of mice to platinum salts. Food Chem Toxicol; 36(3): 199-207.

38. Degussa AG. (1989) Ammoniumtetrachloroplatinate (II) ï acute toxicity after single oral administration in rats. Hanau, Degussa A.G. (Unpublished report No. 863886).

39. Dissanayake CB. (1984) The abundance of Au, Pt, Pd and the mode of heavy metal fixation in highly polluted sediments from the Rhine river near Mainz, West Germany. Int J environ Stud; 22: 109ï 119.

40. Duffield FVP, Yoakum A, Bumgarner J *et al.* (1976) Determination of human body burden baseline data of platinum through autopsy tissue analysis. Environ Health Persp; 15: 131-134.

41. Ensslin AS, Pethran A, Schierl R, Fruhmann G. (1994) Urinary platinum in hospital personnel occupationally exposed to platinum-containing antineoplastic drugs. Int Arch Occup Environ Health; 65: 339-342.

42. Farago ME, Kavanagh P, Blanks R, Kelly J, Kazantzis G, Thornton I, Simpson PR, Cook JM, Parry S, Hall GM. (1998) Platinum concentrations in urban road dust and soil, and in blood and urine in the United Kingdom. Analyst; 123(3): 451-454.

43. Fisher AA. (1986) Dermatitis and discolorations from metals. Contact Dermatitis 3rd ed. Philadelphia; Lea & Febiger: 734-744.

44. Fothergill SJR, Withers DF, Clements FS. (1945) Determination of traces of platinum and palladium in the atmosphere of a platinum refinery. Br J Ind Med; 2: 99-101.

45. Gauggel DL, Sarlo K, Asquith TN. (1993) A proposed screen for evaluating low-molecular- weight chemicals as potential respiratory allergens. J Appl Toxicol; 13: 307-313.

46. Gebel T, Lantzsch H, Plessow K, Dunkelberg H. (1997) Genotoxicity of platinum and palladium compounds in human and bacterial cells. Mutat Res; 389(2-3): 183-190.

47. Goelzer B. (1996) The 1996 William P. Yant Award Lecture: The Harmonized Development of Occupational Hygiene - a Need in Developing Countries. Am Ind Hyg Assoc J; 57: 984.

48. Goldberg ED, Hodge V, Kay P Stallard S, Koide M. (1986) Some comparative marine chemistries of platinum and iridium. Appl Geochem; 1: 227ï 232.

49. Goldberg ED, Koide M. (1990) Understanding the marine chemistries of the platinum metals. Mar Chem; 30: 249ï 257.

50. Gómez B, Palacios MA, Gómez M, Sanchez JL, Morrison G, Rauch S, McLeod C, Ma R, Caroli S, Alimonti A, Petrucci F, Bocca B, Schramel P, Zischka M, Pettersson C, Wass U. (2002) Levels and risk assessment for humans and ecosystems of platinum-group elements in the airborne particles and road dust of some European cities. Sci Total Environ; 299(1-3): 1-19.

51. Granlund M. (1991) Hexaklorplatinasyra och rodiumklorid vid tillverkning av katalysatorer. Report from National Institute of Occupational Health, Umeå. (In Swedish) (Cited in the Health Council of the Netherlands, 2008).

52. Greenwood NN, Earnshaw A. (1997) Chemistry of the elements. London: Pergamon Press, Second Edition. pp. 1144 -1173. ISBN 0 7506 3365 4.

53. Hägg G (1963) Allmän och Oorganisk Kemi, femte uppl. Stockholm: Almqvist & Wiksell, 693-698 (in Swedish) (Cited in the Health Council of the Netherlands, 2008).

54. Hamilton EJ, Minski MJ. (1972/1973) Abundance of the chemical elements in manôs diet and possible relations with environmental factors. Sci Total Environ; 1: 375-394.

55. Hardman RS, Wright CH. (1896) A case of poisoning by chloro-platinite of potassium. Br Med J; 1: 529.

56. Health and Safety Executive (HSE) (1985) Methods for the determination of hazardous substances MDHS 46. Platinum metal and soluble inorganic compounds of platinum in air. HSE Books, UK. ISBN 0717613062.

57. Health and Safety Executive (HSE). (1990) Occupational exposure limits. UK: London, H.M. Stationery Office. (Guidance Note EH 40190).

58. Health and Safety Executive (HSE) (1996) Platinum metal and soluble platinum compounds in air: laboratory method using electrothermal atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. MDHS46/2. Sudbury (Suffolk), England: HSE Books, ISBN 0 7176 1306 2.

59. Health Council of the Netherlands. (2008) Platinum and platinum compounds. Health-based recommended occupational exposure limit. The Hague: HCN; publication no. 2008/12OSH. ISBN 978 90 5549 718 8.

60. Hery M, Gerber JM, Hubert G, Hecht G, Diebold F, Honnert B, Moulut JC. (1994) Exposure to metallic catalyst dust: manufacturing and handling of catalysts in the chemical industry. Ann Occup Hyg; 38: 119-135.

61. Holbrook DJ, Washington ME, Leake HB, Brubaker PE. (1975) Studies on the evaluation of the toxicity of various salts of lead, manganese, platinum, and palladium. Environ Health Persp; 10: 95-101.

62. Holbrook DJ (1976) Assessment of toxicity of automotive metallic emissions. Vol 1. EPA/600/1-76/010a. University of North Carolina, NC, 67 pp.

63. Holbrook DJ, Washington ME, Leake HB, Brubaker PE. (1976). Effects of platinum and palladium salts on parameters of drug metabolism in rat liver. J Toxicol Environ Health; 1: 1067-1079.

64. Holland MK, White IG. (1980) Heavy metals and spermatozoa.1. Inhibition of the motility and metabolism of spermatozoa by metals related to copper. Fertil Steril; 34: 483-489.

65. Holt PG. (1987) Immune and inflammatory function in cigarette smokers. Thorax; 42: 241-249.

66. Hostynek JJ, Hinz RS, Lorence CR, Price M, Guy RH. (1993) Metals and the skin. Crit Rev Toxicol; 23: 171-235.

67. Hsie AW (1981) Structure-mutagenicity analysis with the CHO/HGPRT system. Food Cosmet Toxicol; 19: 617-621.

68. Hughes EG. (1980) Medical surveillance of platinum refinery workers. J Soc Occup Med; 30: 27-30.

69. Hunter D, Milton R, Perry KMA. (1945) Asthma caused by the complex salts of platinum. Br J Ind Med; 2: 92-98.

70. International Agency for Research on Cancer (IARC). (1981) Cisplatin. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some antineoplastic and immunosuppressive agents. Lyon: IARC; 26: 151-164.

71. International Programme on Chemical Safety (IPCS). (1991) Environmental Health Criteria No. 125. Geneva: World Health Organization; pp.167. ISBN 924157125X.

72. Johnson DE, Tillery JB, Prevost RJ. (1975) Levels of platinum, palladium, and lead in populations of southern California. Environ Health Persp; 12: 27-33.

73. Johnson DE, Prevost RJ, Tillery JB, Caman DE, Hosenfeld JM. (1976) Baseline levels of platinum and palladium in human tissue. EPA/600/1-76/019. San Antonio, Texas: Southwest Research Institute. NTIS PB-251 885/0. pp. 252.

74. Johnson NP, Hoeschele JD, Rahn RO, O'Neill JP, Hsie A. (1980) Mutagenicity, cytotoxicity, and DNA binding of platinum(II)-chloroammines in chinese hamster ovary cells. Cancer Res; 40: 1463-1468.

75. Kamboj VP, Kar AB. (1964) Antitesticular effect of metallic and rare earth salts. J Reprod Fertil; 7: 21-28.

76. Kanematsu N, Hara M, Kada T (1980) Rec assay and mutagenicity studies on metal compounds. Mutat Res; 77: 109-116.

77. Kanematsu N, Nakamine H, Fukuta Y, Yasuda JI, Kurenuma S, Shibata KI. (1990) Mutagenicity of cadmium, platinum and rhodium compounds in cultured mammalian cells. J Gifu Dent Soc; 17: 575-581.

78. Kazantzis G. (1990) Hypersensitivity: clinical aspects In: Dayan AD (ed). Immunotoxicity of metals and immunotoxicology. New York, Plenum Press, pp. 67ï 74. ISBN 0306436795.

79. Kirchgessner M, Reichlmayr-Lais AM. (1992) Pt-Gehalte in Milch und Nachkommen von Ratten nach Applikation von Platin in Form von $PtCl_2$ und $PtCl_4$ während der Laktation. J Anim Physiol Anim Nutr ; 68: 151-155. (Cited in the Health Council of the Netherlands, 2008).

80. Kirchgessner M, Bogenrieder A, Reichlmayr-Lais AM. (1993) Pt-Retention in der feto-plazentalen Einheit von graviden Ratten nach unterschiedlich hoher $PtCl_4$- und $Pt^0$-Ingestion. J Anim Physiol Anim Nutr; 69: 151-155. (Cited in the Health Council of the Netherlands, 2008).

81. Koch P, Baum HP. (1996) Contact stomatitis due to palladium and platinum in dental alloys. Contact Dermatitis; 34(4): 253-257.

82. König HP, Hertel RF, Koch W, Rosner G. (1992) Determination of platinum emissions from a three-way catalyst-equipped gasoline engine. Atmos Environ; 26A: 741-745.

83. Lecointe P, Macquet JP, Butour JL, C. Paoletti. (1977) Relative efficiencies of a series of squareplanar platinum(II) compounds on salmonella mutagenesis. Mutat Res; 48: 139-144.

84. Lide DR. (1995) Handbook of Chemistry and Physics 76th ed. New York: CRC Press. ISBN-10: 0849304768. pp. 4-39, 4-40, 4-76, 4-77, 4-79.

85. Liedel NA, Busch KA, Lynch JR. (1977) NIOSH: Occupational Exposure Sampling Strategy Manual (OESSM). U.S. Department of health, education and welfare public health service. Center for disease control. National institute for occupational safety and health. Washington D.C., U.S.: Government printing office.

86. Lindell B. (1997) DECOS and NEG Basis for an Occupational Standard. Platinum. Arbete och Hälsa; 14: 1-65.

87. Linnett PJ, Hughes EG. (1999) 20 years of medical surveillance on exposure to allergenic and non-allergenic platinum compounds: the importance of chemical speciation. Occup Environ Med; 56(3): 191-196.

88. Linnett PJ. (1987) Platinum salt sensitivty. J Mine Med Offic Assoc S Afric; 63: 24-28.

89. Loebenstein JR. (1988) Platinum group metals. In: Minerals yearbook 1987. Vol. 1, Metals and minerals. Washington DC, US Department of the Interior, Bureau of Mines, pp. 689ï 700.

90. Lown BA, Morganti JB, Stineman CH, D´Agostino RB, Massaro EJ. (1980) Tissue organ distribution and behavioral effects of platinum following acute and repeated exposure of the mouse to platinum sulfate. Environ Health Persp; 34: 203-212.

91. Mandervelt C, Clottens FL, Demedts M, Nemery B. (1997) Assessment of the sensitization potential of five metal salts in the murine local lymph node assay. Toxicol; 120(1): 65-73.

92. Massmann W, Opitz H. (1954) Uber Platinallergie. Zentralbl f Arbeitsmed u Arbeitssch; 4: 1-4. (Cited in the Health Council of the Netherlands, 2008).

93. Mastromatteo E. (1983) Platinum, alloys and compounds. Encyclop Occup Health Safety; 2: 1723 -1724.

94. Maynard AD, Northage C, Hemingway M, Bradley SD. (1997) Measurement of short-term exposure to airborne soluble platinum in the platinum industry. Ann Occup Hyg; 41(1): 77-94.

95. Mazzotti F, Sabbioni E, Ponti J, Ghiani M, Fortaner S, Rossi GL. (2002) *In vitro* setting of dose-effect relationships of 32 metal compounds in the Balb/3T3 cell line, as a basis for predicting their carcinogenic potential. Altern Lab Anim; 30(2): 209-217.

96. Merget R, Schultze-Werninghaus G, Muthorst T, Friedrich W, Meier J. (1988) Asthma due to the complex salts of platinum-a cross-sectional survey of workers in a platinum refinery. Clin Allergy; 18: 569-580.

97. Merget R, Schultze-Werninghaus G, Bode F, Bergman E, Zacho W, Meier-Sydow J. (1991) Quantitative skin prick and bronchial provocation tests with platinum salt. Br J Ind Med; 48: 830-837.

98. Merget R, Reineke M, Rueckmann A. (1994) Nonspecific and specific bronchial responsiveness in occupational asthma caused by platinum salts after allergen avoidance. Am J Respir Crit Care Med; 150: 1146-1149.

99. Merget R, Kulzer R, Dierkes Globisch A, Breitstadt R, Gebler. A, Kniffka A. (2000a) Exposure-effect relationship of platinum salt allergy in a catalyst production plant: conclusions from a 5-year prospective cohort study. J Allergy Clin Immunol; 105(2 Pt 1): 364-370.

100. Merget R. (2000b) Occupational platinum salt allergy. Diagnosis, prognosis, prevention and therapy. In: Zereini F, Alt F, editors. Anthropogenic Platinum-Group Element Emissions: Their Impact On Man And Environment. Berlin: Springer Verlag; 2000: 257-265.

101. Merget R, Rosner G. (2001) Evaluation of the health risk of platinum group metals emitted from automotive catalytic converters. Sci Total Environ; 270(1-3): 165-173.

102. Messerschmidt J, Alt F, Tölg G, Angerer J, Schaller KH. (1992) Adsorptive voltammetric procedure for the determination of platinum baseline levels in human body fluids. Fresenius J Anal Chem; 343: 391-394.

103. Migliore L, Frenzilli G, Nesti C, Fortaner S, Sabbioni E. (2002) Cytogenetic and oxidative damage induced in human lymphocytes by platinum, rhodium and palladium compounds. Mutagenesis; 17(5): 411-417.

104. Moore W, Hysell D, Crocker W, J. Stara. (1975a) Biological fate of a single administration of 191Pt in rats following different routes of exposure. Environ Res; 9: 152-158.

105. Moore W, Hysell D, Hall L, Campbell K, Stara J. (1975b) Preliminary studies on the toxicity and metabolism of palladium and platinum. Environ Health Persp; 10: 63-71.

106. Moore W, Malanchuk M, Crocker, Hysell D, Cohen A, Stara JF. (1975c) Whole body retention in rats of different $^{191}$Pt compounds following inhalation exposure. Environ Health Persp; 12: 35-39.

107. Murdoch RD, Pepys J. (1984) Immunological responses to complex salts of platinum. Clin Exp Immunol; 57: 107-114.

108. Murdoch RD, Pepys J, Hughes EG. (1986) IgE antibody responses to platinum group metals: a large scale refinery survey. Br J Ind Med; 43: 37-43.

109. Murdoch RD, Pepys J. (1987) Platinum group metal sensitivity: reactivity to platinum group metal salts in platinum halide salt-sensitive workers. Annals of allergy; 59: 464ï 469.

110. Nakayama H, Ichikawa T. (1997) Occupational contact urticaria syndrome due to rhodium and platinum. In: Amin S, Maibach HI, Lahti A, editors. Contact Urticaria Syndrome. Boca Raton, Fla: CRC: 233-240.

111. National Institute for Occupational Safety and Health (NIOSH). (1994) NIOSH Method 7300. Elements by ICP. NIOSH Manual of Analytical Methods. Fourth Edition, Issue 2. August 15.

112. National Institute for Occupational Safety and Health (NIOSH). (2003) NIOSH Method 7303. Elements by ICP (Hot Block/HCl/HNO3 Ashing) NIOSH Manual of Analytical Methods. Fourth Edition, Issue 1. March 15, 2003. Number PB81-228181, 36 pp.

113. Newman Taylor AJ, Cullinan P, Lympany PA, Harris JM, Dowdeswell RJ, du Bois RM. (1999) Interaction of HLA phenotype and exposure intensity in sensitization to complex platinum salts. Am J Respir Crit Care Med; 160(2): 435-438.

114. Nygren O, Vaughan GT, Florence TM, Morrison GMP, Warner IM, Dare LS. (1990) Determination of platinum in blood by adsorptive voltammetry. Anal Chem; 62: 1637-1640.

115. Nygren O, Lundgren C, Vaughan G, Florence M. (1991) Determination of platinum in biological materials and of occupational exposure to platinum anti-neoplastic drugs. XXVII-CSI Postsymposium specification of elements in environmental and biological science. Loen, Norge, June 16-18.

116. O´Hollaren MT. (1992) Asthma due to metals and metal salts. In: Bardana EJ *et al,* eds. Occupational Asthma. Philadelphia: Hanley & Belfus: 179-188.

117. Occupational Safety and Health Administration (OSHA). (1985) OSHA method ID130SG. Platinum in workplace atmospheres. OSHA Analytical Methods Manual. [Web:] Available from: URL: http://www.osha.gov/dts/sltc/methods/inorganic/id121/id121.pdf [Date of access: 15 January 2011].

118. Occupational Safety and Health Administration (OSHA). (1991) OSHA Method ID121. Metal and metalloid particulates in workplace atmospheres (Atomic absorption). OSHA Analytical Methods Manual. Second Edition, 1991.

119. Parrot JL, Hebert R, Saindelle A, Ruff F. (1969) Platinum and platinosis. Arch Environ Health; 19: 685-691.

120. Paschal DC, Ting BG, Morrow JC, Pirkle JL, Jackson RJ, Sampson EJ, Miller DT. (1998) Trace metals in urine of United States residents: reference range concentrations. Environ Res; 76(1): 53-59.

121. Petrucci F, Violante N, Senofonte O, Cristaudo A, Di Gregorio M, Forte G. (2005) Biomonitoring of a worker population exposed to platinum dust in a catalyst production plant. Occup Environ Med; 62(1): 27-33.

122. Raulf-Heimsoth M, Merget R, Rihs HP, Fohring M, Liebers V, Gellert B. (2000) T-cell receptor repertoire expression in workers with occupational asthma due to platinum salt. Eur Respir J; 16(5): 871-878.

123. Raulf-Heimsoth M, Liebers V, Kutzner N, Fohring M, Liebers V, Gellert B. (2001) Platinum salt induced T-cell stimulation expression of cell surface molecules and cytokine release. Atemw Lungenkrh; 27(7): 337-339.

124. Reichlmayr-Lais AM, Kirchgessner M, Bader R. (1992) Dose-response relationships of alimentary $PtCl_2$ and $PtCl_4$ in growing rats. J Trace Elem Electrolytes Health Dis; 6: 183-187.

125. Renner H, Schumuckler G. (1991) Platinum group metals. In: Merian E. (Ed.), Metals and their compounds in the environment. VCH Verlagsgesellschaft, Weinheim. pp. 1136ï 1151.

126. Roberts AE. Platinosis. (1951) Arch Ind Hyg Occup Med; 4: 549-559.

127. Roshchin AV, Veselov VG, Panova AI. (1984) Industrial toxicology of metals of the platinum group. J Hyg Epidemiol Microbiol Immunol; 28: 17-24.

128. Rosner G, Merget R. (1990) Allergenic potential of platinum compounds. In Immunotoxicity of Metals and Immunotoxicology (edited by Dayan AD, et al.). New York, Plenum Press: 93-102. ISBN 0306436795.

129. Rosner G, Merget R. (2000) Evaluation of the health risk of platinum emissions from automotive emission control catalysts. In: Zereini F, Alt F, editors. Anthropogenic Platinum-Group Element Emissions. Berlin: Springer Verlag; 2000: 267-281.

130. Saindelle A, Ruff F. (1969) Histamine release by sodium chloroplatinate. Br J Pharmacol; 35: 313-321.

131. Sandhu S. (1979) Evaluation of the mutagenic potentials of platinum compounds. US Environmental Protection Agency, North Carolina, EPA-600/1-79-033, NTIS Accession Number PB81-228181, 36 pp.

132. Santucci B, Valenzano C, de Rocco M, Cristaudo A. (2000) Platinum in the environment: frequency of reactions to platinum-group elements in patients with dermatitis and urticaria. Contact Dermatitis; 43(6): 333-338.

133. Sauerwald P. Die industrielle Platinallergie. (1961) Zeitschr Ges Hyg Ihre Grenzgeb; 7: 738-742. (Cited in the Health Council of the Netherlands, 2008).

134. Schaller KH, Angerer J, Alt F, Messerschmidt, Weber A. (1992) The determination of platinum in blood and urine as a tool for the biological monitoring of internal exposure. Proc SPIE-Int Soc Opt Eng 1993, International Conference on Monitoring of Toxic Chemicals and Biomarkers; 1716: 498-504.

135. Schierl R, Fries HG, van de Weyer C, Fruhmann G. (1998) Urinary excretion of platinum from platinum industry workers. Occup Environ Med; 55(2): 138-140.

136. Schuppe HC, Haas-Raida D, Kulig J, Bömer U, Gleichmann E, Kind P. (1992) T-cell-dependent popliteal lymph node reactions to platinum compounds in mice. Int Arch Allergy Immunol; 97: 308-314.

137. Schuppe HC, Kulig J, Kuhn U, Lempertz U, Kind P, Knop J. (1997a) Immunostimulatory effects of platinum compounds: correlation between sensitizing properties in vivo and modulation of receptor mediated endocytosis in vitro. Int Arch Allergy Immunol; 112(2): 125-132.

138. Schuppe HC, Kulig J, Lerchenmuller C, Becker D, Gleichmann E, Kind P. (1997b) Contact hypersensitivity to disodium hexachloroplatinate in mice. Toxicol Lett; 93(2-3): 125-133.

139. Schutyser P, Govaerts A, Dams R, Hoste J. (1977) Neutron activation analysis of platinum metals in airborne particulate matter. J Radioanal Chem; 37: 651-660.

140. Sheard C. (1955) Contact dermatitis from platinum and related metals. AMA Arch Dermatol; 71: 357-360.

141. Shi ZC. (1987) Platinosis. Proc ICMR Semin 1988 and Proc Asia-Pac Symp. Environ Occup Toxico; 1987: 133-135.

142. Shima S, Yoshida T, Tachikawa S, Kato Y, Miki T, Hidaka K, Taniwaki H, Ito T. (1984) Bronchial asthma due to inhaled chloroplatinate. Jap J Ind Health; 26: 500-509.

143. Skinner PE. (1989) Improvements in platinum plating. Platinum Met Rev; 33: 102-105.

144. Smith BL, Hanna ML, Taylor RT (1984) Induced resistance to platinum in chinese hamster ovary cells. J Environ Sci Health; A19: 267-298.

145. Sora S, Magni GE (1988) Induction of meiotic chromosomal malsegregation in yeast. Mutat Res; 201: 375-384.

146. South Africa. (1993) Occupational Health and Safety Act (OHSA), No. 85 of 1993. Pretoria: Government Printer.

147. South Africa. (1995) Hazardous Chemical Substances Regulations (HCSR), Regulation 1779 of 25. August, 1995. Pretoria: Government Printer.

148. South Africa. (1996) Mine Health and Safety Act (MHSA), No. 26 of 1996. Pretoria: Government Printer. 2006 Occupational Exposure Limits For Airborne Pollutants.

149. Sykes TR, Stephens-Newsham LG, Noujaim AA. (1985) In vitro binding of platinum compounds to human transferrin. Res Commun Chem Pathol Pharmacol; 50: 387-394.

150. Taubler J. (1977) Allergic response to platinum and palladium complexes. Determination of no-effect level. US Environmental Protection Agency, North Carolina, EPA-600/1-77-039, NTIS Accession Number PB 271 659, 81 pp.

151. Taylor RT, Happe JA, Wu R (1978) Methylcobalamin methylation of chloroplatinate: bound chloride, valence state, and relative mutagenicity. J Environ Sci Health; A13: 707-723.

152. Taylor RT, Carver JH, Hanna ML, Wandres DL. (1979a) Platinum-induced mutations to 8-azaguanine resistance in chinese hamster ovary cells. Mutat Res; 67: 65-80.

153. Taylor RT, Happe JA, Hanna ML, Wu R. (1979b) Platinum tetrachloride: mutagenicity and methylation with methylcobalamin. J Environ Sci Health; A14: 87-109.

154. Taylor RT, Wu R, Hanna ML (1985) Induced reversion of a chinese hamster ovary triple auxotroph. Mutat Res; 151: 293-308.

155. Trynda L, Kuduk-Jaworska J. (1994) Impact of $K_2PtCl_4$ on the structure of human serum albumin and its binding ability of heme and bilirubin. J Inorg Biochem; 53: 249-261.

156. Uno Y, Morita M (1993) Mutagenic activity of some platinum and palladium complexes. Mutat Res; 298: 269-275.

157. Van Den Berg CMG, Jacinto GS. (1988) The determination of platinum in sea water by adsorptive cathodic stripping voltammetry. Analytica chimica acta; 211: 129ï 139.

158. Vaughan GT, Florence TM. (1992) Platinum in the human diet, blood, hair and excreta. Sci Tot Environ; 111: 47ï 58.

159. Venables KM, Dally MB, Nunn AJ, Stevens JF, Stephens R, Farrer N, Hunter, JV, Stewart M, Hughes EG, Newman Taylor AJ. (1989) Smoking and occupational allergy in workers in a platinum refinery. Br Med J; 299: 939-942.

160. Ward JM, Young DM, Fauvie KA. (1976) Comparative nephrotoxicity of platinum cancer therapeutic agents. Canc treat rep; 60: 1675ï 1678.

161. Weber A, Schaller KH, Angerer J, Alt F, Schmidt M, Weltle D. (1991) Objektivierung und Quantifizierung einer beruflichen Platinbelastung beim Umgang mit platinhaltigen Katalysatoren. Verh Dtsch Ges Arbeitsmed; 31: 611-614. (Cited in the Health Council of the Netherlands, 2008).

162. Wei C, Morrison GM. (1994) Platinum in road dusts and urban river sediments. Sci Tot Environ; 146/147: 169-174.

163. Wester PO. (1965) Concentration of 24 trace elements in human heart tissue determined by neutron activation analysis. Scand J Clin Lab Invest; 17: 357-370.

164. White RP, Cordasco EM. (1988) Occupational asthma. In: Zenz C, ed.Occupational Medicine. Principles and Practical Applications 2nd ed. Chicago: Year Book Medical Publ, 1988: 235-242. ISBN 9170454477.

165. Wittsiepe J, Schrey P, Wilhelm M, Begerow J, Dunemann L. (2003) Dietary intake of platinum and gold by children from Germany using duplicate portion sampling. J Trace Elem Med Biol; 17(2): 117-122.

166. Woodruff RC, Valencia R, Lyman RF, Earle BA, Boyce JT. (1980) The mutagenic effect of platinum compounds in Drosophila melanogaster. Environ Mutagen; 2: 133-138.

167. Woolf AD, Ebert TH. (1991) Toxicity after self-poisoning by ingestion of potassium chloroplatinite. Clin Toxicol; 29: 467-472.

168. World Health Organization (WHO). (1991) International Programme on Chemical Safety. Geneva, Switzerland: Environmental Health Criteria No. 125.

169. World Health Organization (WHO). (1999) Hazard Prevention and Control in the Work Environment: Airborne Dust. Geneva, Switzerland: WHO/SDE/OEH/99.14. pp. ix-xxiii.

170. World Health Organization (WHO). (2000) Inorganic pollutants: Platinum. In: Air quality guidelines for Europe. Copenhagen. WHO: 166-169.

171. Yoshinaga J, Matsuo N, Imai H, Nakazawa M, Suzuki T. (1990) Application of inductively coupled plasma mass spectrometry (ICP-MS) to multi-element analysis of human organs. Intern J Environ Anal Chem; 41: 27-38.

172. Ysart G, Miller P, Crews H, Robb P, Baxter M, De L'Argy C, Lofthouse S, Sargent C, Harrison N. (1999) Dietary exposure estimates of 30 elements from the UK Total Diet Study. Food Addit Contam; 16(9): 391-403.

173. Zeisler R, Greenberg RR. (1988) Determination of baseline platinum levels in biological materials. In: Br.tter P, Schramel P, eds. Trace Elem Anal Chem Med Bio. Berlin: Walter de Gruyter & co: 297-303.

174. Zereini F, Alt F, Messerschmidt J, von Bohlen A, Liebl K, Puttmann W. (2004) Concentration and distribution of platinum group elements (Pt, Pd, Rh) in airborne particulate matter in Frankfurt am Main, Germany. Environ Sci Technol; 38(6): 1686-1692.

175. Zhong W, Zhang Q, Yan Y, Yue S, Zhang B, Tang W. (1997a) Interaction of sodium chloroplatinate and iproplatin with metallothionein *in vivo*. J Inorg Biochem; 66(3): 159-164.

176. Zhong W, Zhang Q, Yan Y, Yue S, Zhang B, Tang W. (1997b) Reaction of a platinum(IV) complex with native Cd,Zn-metallothionein *in vitro*. J Inorg Biochem; 66(3): 179-185.

# CHAPTER 3: ARTICLE - Exposure of South African platinum refinery workers to soluble platinum during non-routine operations: a task-based approach.

## INSTRUCTIONS FOR AUTHORS: ANNALS OF OCCUPATIONAL HYGIENE

The *Annals of Occupational Hygiene* is one of the world's top research journals on hazards and risks to health resulting from work. The journal is particularly interested in recognition, quantification, management, communication, and control of risk. It includes papers on basic mechanisms, human aspects and technology, and on environmental risks to humans when these are linked to risks at work. Researchers wishing to submit their studies for publication in the *Annals of Occupational Hygiene* should follow the guidelines below:

1. *Annals of Occupational Hygiene* publishes original research and development material that helps reduce risk of ill-health resulting from work, and welcomes submissions in these areas.
2. The usual categories that *Annals of Occupational Hygiene* publish are Commentaries, Papers (including Review Articles), and Letters to the Editor.
3. The Annals aims to conform to the Code of Conduct and the Guidelines of the Committee on Publication Ethics (COPE).
4. Submitted material must be original, and not under consideration elsewhere.
5. Manuscripts must be in English. British or American styles and spelling may be used, but should be used consistently.
6. Submissions must be as brief as possible, consistent and clear. If this length is more than 5000 words, a statement must be included justifying the extra length.
7. The title should clearly summarise the subject of the paper. The keywords should be a list of words and phrases which an internet searcher might use who is interested in the topic and findings of the paper.
8. Persons should only be named as authors if they have made significant identifiable intellectual contributions to the work; other contributions may be recognised by acknowledgement at the end of the submission.
9. Papers should generally conform to the pattern: Introduction, Methods, Results, Discussion, and Conclusions. A paper must be prefaced by an abstract of the argument and findings, which may also be arranged under the same headings.
10. The quality of the data and analysis must always be good enough to justify the inferences and conclusions drawn.
11. SI units must be used, though their equivalent in other systems may be given as well.

12. The revised version of the paper should be accompanied by high-resolution electronic copies of figures (photographs, diagrams and charts). They should be about the size they are to be reproduced, with font size at least 6 point, using the standard Adobe set of fonts.
13. Tables should be numbered consecutively and footnotes should be typed below the table and should be referred to by superscript lowercase letters.
14. References should be listed at the end of the paper, in alphabetical order by name of first author, using the Vancouver Style of abbreviation and punctuation. ISBNs should be given for books and other publications where appropriate. Personal communications, if essential, should be cited in the text in the form (Professor S.M. Rappaport, University of California). 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.

# Evaluation of exposure to airborne soluble platinum in a precious metal refinery during non-routine operations

**AMELDA VOS*, PETRUS J. LAUBSCHER, JOHANNES L. DU PLESSIS and CASPER J. BADENHORST**

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

**ABSTRACT**

**Objectives: The objectives of this study were to assess personal and area exposure of workers to platinum at a South African precious metals refinery during non-routine operations. Methods: Both area and personal exposure levels were measured during the stock take period. The refinery was systematically dismantled and cleaned out during which critical tasks were measured for the duration of the activity. Personal exposure samples were collected with a personal inhalable IOM sampler operating at a sampling volume of 2 L/min. Area exposure levels were measured by means of BUCKAir high volume samplers operating at a sampling volume of 20 L/min. Samples were analysed for platinum according to MDHS method 46/2, using inductively coupled plasma-mass spectrometry. Results: The personal platinum exposure concentrations ranged between 0.004-20.479 µg/m$^3$ and between 0.0004-5.752 µg/m$^3$ for area exposure. 21% of personal exposure measurements and 10% of area exposure measurements exceeded the OEL of 2 µg/m$^3$. The mean personal exposure levels for the production subgroup (2.739 µg/m$^3$) were significantly higher (p=0.033) compared to the engineering subgroup's mean personal exposure levels (0.393 µg/m$^3$). The mean total personal exposure levels (1.813 µg/m$^3$) were higher compared to the mean total area exposure levels (0.583 µg/m$^3$) and differed statistically (p=0.004). Open face (0.725 µg/m$^3$) versus closed face (0.441 µg/m$^3$) mean exposure levels did not differ significantly (p=0.579). Conclusions: High levels of personal exposure during stock take were most probably as a result of increased contact with platinum since the normally enclosed process and system was dismantled causing platinum compounds to become airborne.**

Keywords: platinum exposure; personal sampling, area sampling; non-operational period; precious metals refinery; inductively coupled plasma-mass spectrometry; MDHS 46/2.

*Author to whom correspondence should be addressed.
Tel: +27-072 4403328; e-mail: AVos@angloplat.com

## INTRODUCTION

Mining, refining and processing are the three primary industrial sources that contribute to occupational exposure to platinum. Of the three sources refining caused the highest occupational exposure risk to workers (WHO, 2000).

The platinum refining process involves exposure to chloroplatinate salts which are potent skin and respiratory sensitisers that can result in the clinical syndrome of platinum salt sensitivity They induce symptoms typical of a type I allergy, the most significant of which is asthma. Even in modern, well-controlled working environments, about 1% (40 out of 4000) of workers exposed to chloroplatinates are sensitised annually (Bullock, 2010). Once sensitised, the concentration that elicits an adverse response is lower and complete removal of the sensitised worker from the platinum industry where chloroplatinates are present may be necessary (Lindell, 1997). Symptoms of sensitisation do not appear immediately, and a subsequent platinum salt exposure that elicits a response may occur much later, making it more difficult to find the exact exposure conditions that cause sensitisation.

Elicitation of allergic symptoms normally occurs at platinum air levels above 2 µg/m$^3$, but cases have been reported where sensitisation occurred at platinum levels as low as 0.05 µg/m$^3$ (WHO, 2000; Health Council of the Netherlands, 2008). A science-based threshold of exposure that causes sensitisation has not yet been found. This is a matter of increasing concern and improved control measures such as substitution of non-sensitising platinum species, enclosed and automated processing, optimal ventilation, occupational hygiene monitoring, etc., together with close medical surveillance needs to be implemented in the platinum industry (Lindell, 1997; Health Council of the Netherlands, 2008; Bullock, 2010). Several studies (Fothergill *et al.,* 1945; Hunter *et al.*, 1945; Johnson *et al.*, 1976; Shi, 1987; Merget *et al.*, 1988; Baker *et al.*, 1990; Bolm-Audorff *et al.,* 1992; HSE, 1996) documented platinum air levels in refineries to be between 0.01-80000 µg/m$^3$ with the extremely high levels of platinum (5000-80000 µg/m$^3$) reported in a badly ventilated platinum refinery in China (Shi, 1987). The average platinum concentration was below 10000 µg/m$^3$ at most places measured (Lindell, 1997; Health Council of the Netherlands, 2008).

Research shows that platinum exposure studies were mostly done during production periods, however, the extent of exposure during non-operational, non-routine stock take activities was unknown. Therefore, the objective of the study was to assess and quantify personal and area platinum exposure levels of workers at a South African precious metals refinery during this non-operational period.

## METHOD

### Site description

The company is involved in the recovery of platinum and other precious metals from high grade feed received from a precious base metals refinery. The majority of platinum refining is carried out by dissolution, followed by solvent extraction, precipitation of the salt, and reduction to give the pure metal. Incoming metallic materials are initially graded, and prepared for dissolution. This may involve a number of processes, depending on the initial state of the feed. Graded metallic materials are dissolved in aqua regia and the resulting solution transported in an enclosed system to a solvent extraction plant. Ammonium chloride is then added to the solution, leading to a precipitate of ammonium chloroplatinate forming. This is filtered out in a boxed vacuum filter. The precipitate is removed by hand scoop from the filter while still wet and transferred to skips. It is then calcined in a furnace to give platinum sponge. Stock take for the platinum refinery under study commenced on 18 January 2010 and ended 22 February 2010. Increased emphasis was placed on flushing plant equipment rather than dismantling it. The aim was to dismantle 10% of what previously was dismantled to reduce the risk of exposing employees to soluble platinum salts, to reduce the chance of damaging plant equipment and for cost and time saving purposes.

### Sampling equipment

Aerosol sampling included the use of both personal and area exposure samplers. Personal exposure sampling consisted of an IOM sampling head housing a 25 mm filter cassette with a mixed cellulose filter (MCE) for the collection of inhalable airborne particles. The sampling head was clipped in the workerôs breathing zone and attached to a GilAir 3 personal sampling pump calibrated with a Gilian Gilibrator-2 primary flow calibrator (range: 20cc-6 L/min) to aspirate at 2 L/min. The IOM effectively traps particles up to 100 µm in aerodynamic diameter and closely simulates the manner in which airborne workplace particles are inhaled through the nose and mouth. These pumps compensate for external conditions and filter loading to give a constant sampling flow rate. Area exposure sampling was conducted by means of BUCKAir high volume samplers fitted with 47 mm MCE filter cassettes. The high volume samplers were calibrated with Gilian Gilibrator-2 primary flow calibrator (range: 2-30 L/min) to operate at a sampling volume of 20L/min. The sampling heads were positioned at about head height and as near as possible to the work location or failing this as near as is possible to major sources of airborne dust to which workers were exposed to during stock take activities. Both the cassette and the filter (25 and 47 mm filter cassettes) are pre and post-weighed as a single unit, and consequently all particles collected, even larger ones, are included in the analysis.

**Sampling procedure**

Sampling was conducted in accordance with the stock take schedule and scope and included a roster for the systematic dismantling and cleaning of the refinery, following the process flow. A target population of maximum five fitters and five operators per area were identified, responsible for dismantling and cleaning plant equipment respectively. The sampling strategy was based on the identification and sampling of employees presumed to have the highest exposure risk. The Occupational Exposure Sampling Strategy Manual (OESSM) refers to this as the ñmaximum risk employeesò (Liedel *et al.*, 1977). The selection of the maximum risk employees was done with reasonable certainty since the employees sampled were working closest to the source of exposure. The further a personôs location from the source the lower the possibility of significant exposure since air pollutants dilute in the air of the work area. Sampling was conducted for the total duration of the task consisting of single sample measurements.

**Analysis of samples**

Personal and area samples were collected and analysed according to the method for the determination of hazardous substances 46/2 (MDHS 46/2). The filters and collected samples were treated with 5 mL of 0.07 M hydrochloric acid and agitated by mechanical shaking. The leach solution was then filtered under suction through a MCE membrane filter of 0.8 µm mean pore diameter and diluted to 10 mL. The resultant solution was analysed by means of inductively coupled plasma-mass spectrometry (ICP-MS) giving an airborne detection limit for soluble platinum in the order of 0.01 µg/m$^3$, providing the sensitivity necessary to detect low levels of soluble platinum. (HSE, 1996). The method has shown to be suitable for use with sampling times in the range 30 minutes to 8 hours for analysis by IPC-MS.

**Statistical analysis**

All results were statistically analysed using Statistica Version 8.0 (Statsoft Inc., 2009). Descriptive statistics were utilised to determine the distribution (mean, median, minimum, maximum, the lower and upper quartile and standard deviation) of all obtained results. Inter-personal (production versus engineering), inter-area (open face sampling versus closed face sampling) and inter-exposure (personal versus area) results were compared for statistical significance utilising the Mann-Whitney U test since the sample groups are independent and no assumptions about the distribution of the data (e.g., normality) were made. Between work areas exposure results were tested for statistical significance using the Kruskal-Wallis test since more than two sample groups were compared. All results with a $p < 0.05$ were considered to be statistically significant.

## RESULTS

A total of thirty eight (n=38) personal platinum samples were collected, consisting of a sampled engineering (n=15) and production (n=23) subgroup. Out of the thirty eight personal samples taken in total, 21% of the samplesô concentrations exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) and ranged between 0.004-20.479 µg/m$^3$. A total of twenty (n=20) area platinum samples were collected, consisting of open (n=10) and closed face (n=10) sampling. Out of the twenty area samples taken in total, 10% of the samplesô concentrations exceeded the OEL of 2 µg/m$^3$ and ranged between 0.0004-5.752 µg/m$^3$.

Table 1 contains results for the sampled engineering subgroup with personal platinum exposure levels ranging from 0.004-3.916 µg/m$^3$. 7% of the levels exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) with the highest exposure level obtained in Bay 5 (3.916 µg/m$^3$).

Table 1. Personal soluble platinum exposure levels for the engineering subgroup

| Group | Work Area | Process | Tasks | Exposure TWA (µg/m$^3$) |
|---|---|---|---|---|
| Engineering | Bay 2 | Revert dissolve area | Dismantling of reducer | 0.106 |
| Engineering | Bay 2 | Revert dissolve area | Dismantling of riser pipe | 0.130 |
| Engineering | Bay 2 | Pd feed preparation | Dismantling reducer, elbow and 2 catch pots | 0.352 |
| Engineering | Bay 3 | Pt sidestream | Dismantling tank modules | 0.156 |
| Engineering | Bay 3 | Pt sidestream | Dismantling tank manholes | 0.216 |
| Engineering | Bay 3 | Pd sidestream | Dismantling of main draught line manholes | 0.849 |
| Engineering | Bay 5 | Muffle operations | Reassembling manufolds on muffles | 0.005 |
| Engineering | Bay 5 | Muffle operations | Dismantling muffles | 3.916 |
| Engineering | Level 3 | Forge and dispatch | Dismantling Hoppers | 0.029 |
| Engineering | Level 3 | Sampling area | Dismantling FICO sampler | 0.054 |
| Engineering | Level 3 | Calcination | Dismantling muffles and reduction ovens | 0.066 |
| Engineering | VRP plant | Residue handling | Dismantling of dryer | 0.007 |
| Engineering | RHD plant | IM draught system | Dismantling of core scrubber and demister | 0.004 |
| Engineering | RHD plant | RHD DETA handling | Dismantling manufolds on muffles | 0.005 |
| Engineering | AU plant | Gold solvent extraction | Dismantling tanks | 0.007 |

VRP = Value Recovery Plant; RHD = Rhodium; AU = Gold; Pd = Palladium; Pt = Platinum; IM = Insoluble Metals Operations; DETA = Diethylenetriamine; FICO = Final concentrate

The sampled production subgroupôs personal platinum exposure levels (Table 2) ranged from 0.010-20.479 µg/m$^3$. 30% of the levels exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) with the highest exposure level reported for Bay 3 (20.479 µg/m$^3$).

Figure 1 illustrates the distribution for personal exposure and includes total, engineering and productionôs platinum exposure levels. It can be noted that the average exposure levels (mean: 2.739 $\pm$ 5.644 µg/m$^3$) and interquartile range (0.031-2.507 µg/m$^3$) for the production subgroup is significantly higher compared to the average engineering subgroupôs exposure levels (mean: 0.393 $\pm$ 0.999 µg/m$^3$) and interquartile range (0.007-0.216 µg/m$^3$) (Figure 1 and Table 5). A statistical difference (p=0.033) between the engineering and production subgroupôs exposure levels is reported in Table 7.

Table 2. Personal soluble platinum exposure levels for the production subgroup

| Group | Work Area | Process | Tasks | Exposure TWA (µg/m$^3$) |
|---|---|---|---|---|
| Production | Bay 2 | Revert dissolve area | Scrubbing tanks | 2.119 |
| Production | Bay 2 | Revert dissolve area | Cleaning gloveboxes | 19.565 |
| Production | Bay 3 | Pd sidestream | Transferring residues into skips | 0.342 |
| Production | Bay 3 | Pd sidestream | Digging out sump residues | 1.092 |
| Production | Bay 3 | Pt sidestream | Removing module filters | 2.507 |
| Production | Bay 3 | Os sidestream | Digging out sump residues | 3.732 |
| Production | Bay 3 | Pd sidestream | Digging out main draught line residues | 20.479 |
| Production | Bay 5 | Muffle operations | Cleaning muffles | 0.736 |
| Production | Bay 5 | Muffle operations | Cleaning muffles | 1.055 |
| Production | Bay 5 | Muffle operations | Cleaning muffles | 1.227 |
| Production | Bay 5 | Muffle operations | Cleaning muffles | 5.544 |
| Production | Level 3 | Calcination/Sponge | Cleaning skips and equipment | 0.012 |
| Production | Level 3 | preparation | Cleaning muffles | 0.016 |
| Production | Level 3 | Sampling Area | Transporting FICO hoppers | 0.093 |
| Production | VRP | Spillage treatment | Digging out sump residues | 0.010 |
| Production | VRP | Spillage treatment | Digging out sump residues | 0.207 |
| Production | VRP | Residue handling | Cleaning dust extraction fan filters | 0.904 |
| Production | VRP | Residue handling | Cleaning dust extraction fan filters | 3.242 |
| Production | RHD | RHD DETA handling | Cleaning muffles | 0.012 |
| Production | AU Plant | Gold solvent extraction | Cleaning vacuum and draught headers | 0.016 |
| Production | AU Plant | Gold solvent extraction | Cleaning lines, tanks and gloveboxes | 0.031 |
| Production | Solvex | Draught system | Cleaning demister | 0.034 |
| Production | SHE Services | PPE maintenance | Cleaning PPE | 0.036 |

VRP = Value Recovery Plant; RHD = Rhodium; AU = Gold; SHE = Safety, Health, Environment; Pd = Palladium; Pt = Platinum; Os = Osmium; DETA = Diethylenetriamine; PPE = Personal Protective Equipment; FICO = Final concentrate

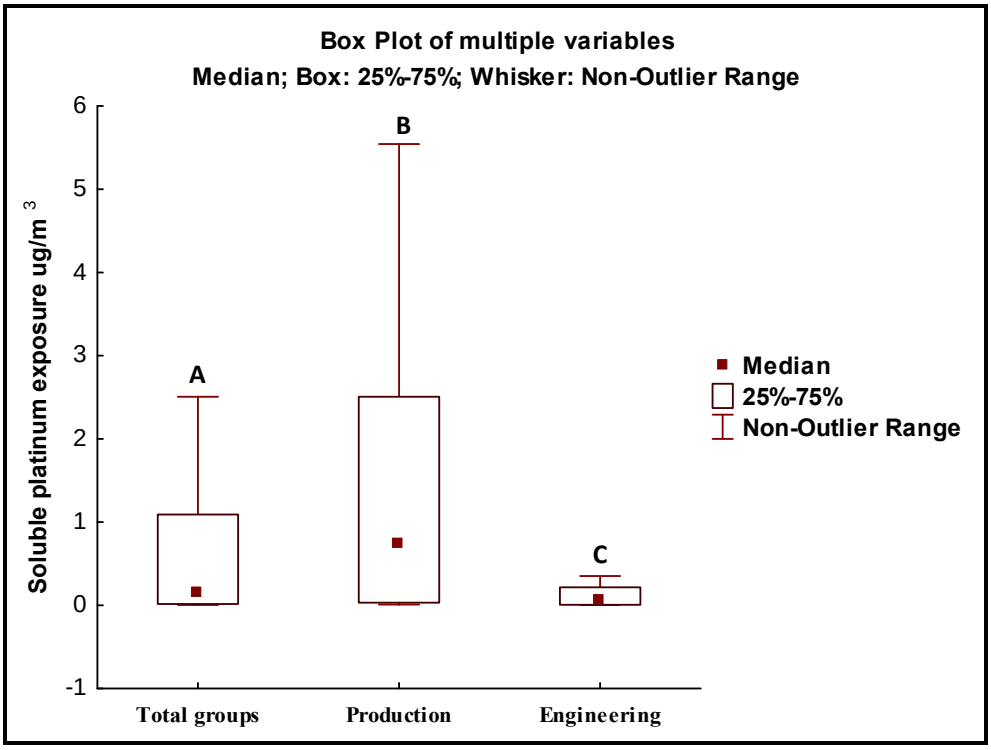


Fig. 1. Box and whisker plots plots illustrating personal platinum exposure for (A) all groups (subgroup B and C), (B) the production and (C) engineering subgroup

The area platinum exposure levels for open face monitoring (Table 3) ranged from 0.0004-5.752 µg/m$^3$. 10% of the results exceeded the OEL with the highest exposure level reported for Bay 5 (5.752 µg/m$^3$).

Table 3. Area soluble platinum exposure levels utilising open face sampling

| Work Area | Process | Tasks performed in this area | Exposure TWA (µg/m$^3$) |
|---|---|---|---|
| Bay 2 | Revert dissolve area | Scrubbing tanks<br>Cleaning gloveboxes<br>Dismantling of reducer<br>Dismantling of riser pipe | 0.118 |
| Bay 2 | Pd feed preparation | Dismantling reducer, elbow and 2 catch pots | 0.028 |
| Bay 3 | Pt sidestream | Removing module filters<br>Dismantling tank modules<br>Dismantling tank manholes | 1.317 |
| Bay 3 | Pd sidestream | Digging out main draught line residues<br>Dismantling of main draught line manholes | 0.019 |
| Bay 3 | Pd and Os sidestream | Digging out sump residues<br>Transferring residues into skips | 0.005 |
| Bay 5 | Muffle operations | Cleaning muffles | 5.752 |
| Level 3 | Calcination | Cleaning muffles | 0.008 |
| | Sponge Preparation | Cleaning skips and equipment<br>Dismantling muffles and reduction ovens | |
| VRP plant | Residue handling | Cleaning dust extraction fan filters | 0.008 |
| RHD plant | IM draught system | Dismantling of core scrubber and demister | 0.001 |
| RHD plant | RHD DETA handling | Cleaning muffles<br>Dismantling manufolds on muffles | 0.0004 |

VRP = Value Recovery Plant; RHD = Rhodium; Pd = Palladium; Pt = Platinum; Os = Osmium; DETA = Diethylenetriamine

The area platinum exposure levels for closed face monitoring (Table 4) ranged from 0.0004-3.581 µg/m$^3$. 10% of the results exceeded the OEL with the highest exposure level reported for Bay 5 (3.581 µg/m$^3$).

Table 4. Area soluble platinum exposure levels utilising closed face sampling

| Work Area | Process | Tasks conducted in this area | Exposure TWA (µg/m$^3$) |
|---|---|---|---|
| Bay 2 | Revert dissolve area | Scrubbing tanks<br>Cleaning gloveboxes<br>Dismantling of reducer and riser pipe | 0.106 |
| Bay 2 | Pd feed preparation | Dismantling reducer, elbow and 2 catch pots | 0.016 |
| Bay 3 | Pt sidestream | Dismantling tank modules and manholes<br>Removing module filters | 0.689 |
| Bay 3 | Pd sidestream | Digging out main draught line residues<br>Dismantling of main draught line manholes | 0.012 |
| Bay 3 | Pd and Os sidestream | Digging out sump residues<br>Transferring residues into skips | 0.004 |
| Bay 5 | Muffle operations | Cleaning muffles | 3.581 |
| Level 3 | Calcination | Cleaning muffles | 0.002 |
| | Sponge Preparation | Cleaning skips and equipment<br>Dismantling muffles and reduction ovens | |
| VRP plant | Residue handling | Cleaning dust extraction fan filters<br>Dismantling of dryer | 0.003 |
| RHD plant | IM draught system | Dismantling of core scrubber and demister | 0.001 |
| RHD plant | RHD DETA handling | Cleaning muffles<br>Dismantling manufolds on muffles | 0.0004 |

VRP = Value Recovery Plant; RHD = Rhodium; Pd = Palladium; Pt = Platinum; Os = Osmium; DETA = Diethylenetriamine;

Figure 2 illustrates the distribution for area exposure and includes total, open and closed face platinum exposure levels. It can be noted that the average exposure levels and interquartile range for open (mean: 0.725 ± 1.813 µg/m$^3$; range 0.005-0.118 µg/m$^3$) and closed face sampling (mean: 0.441 ± 1.123 µg/m$^3$; range 0.002-0.105 µg/m$^3$) did not differ much (Fig. 2 and Table 5). It is evident from statistical analysis that there is no statistical difference (p=0.579) between open and closed face sampling results (Table 7).

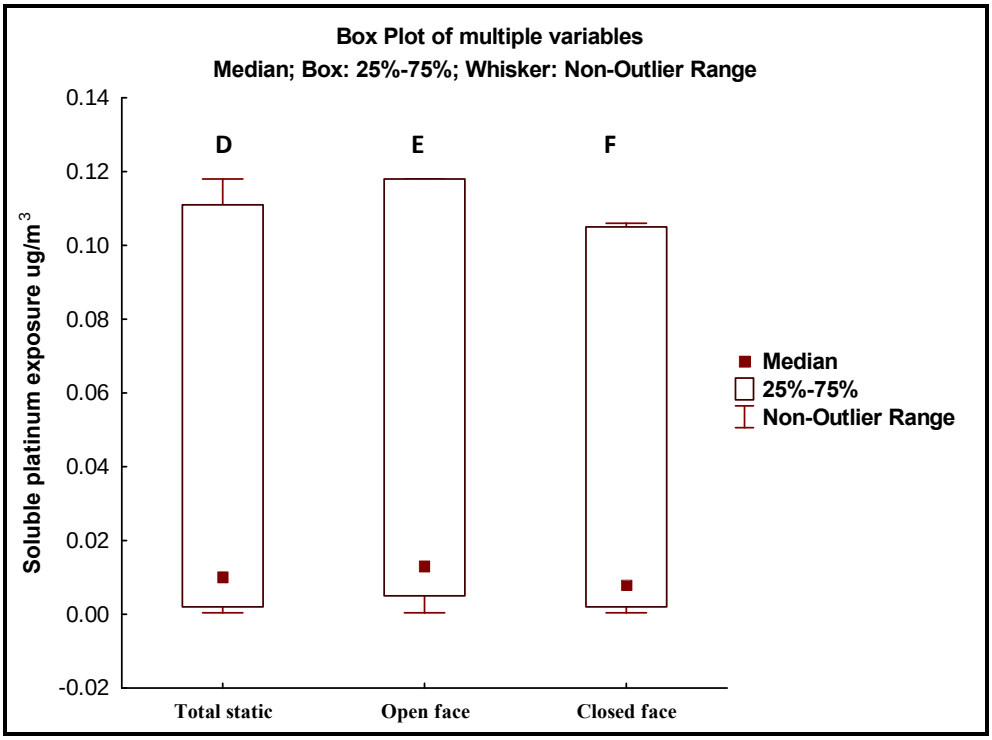


Fig. 2. Box and whisker plots plots illustrating (D) total area (subgroup E and F), (E) open face and (F) closed face platinum exposure

Figure 3 illustrates that the total personal exposure levels and interquartile range (mean: 1.813 ± 4.546 µg/m$^3$; range 0.016-1.092 µg/m$^3$) are higher compared to the total area exposure levels and interquartile range (mean: 0.583 ± 1.475 µg/m$^3$; range 0.002-0.111 µg/m$^3$) (Table 5).

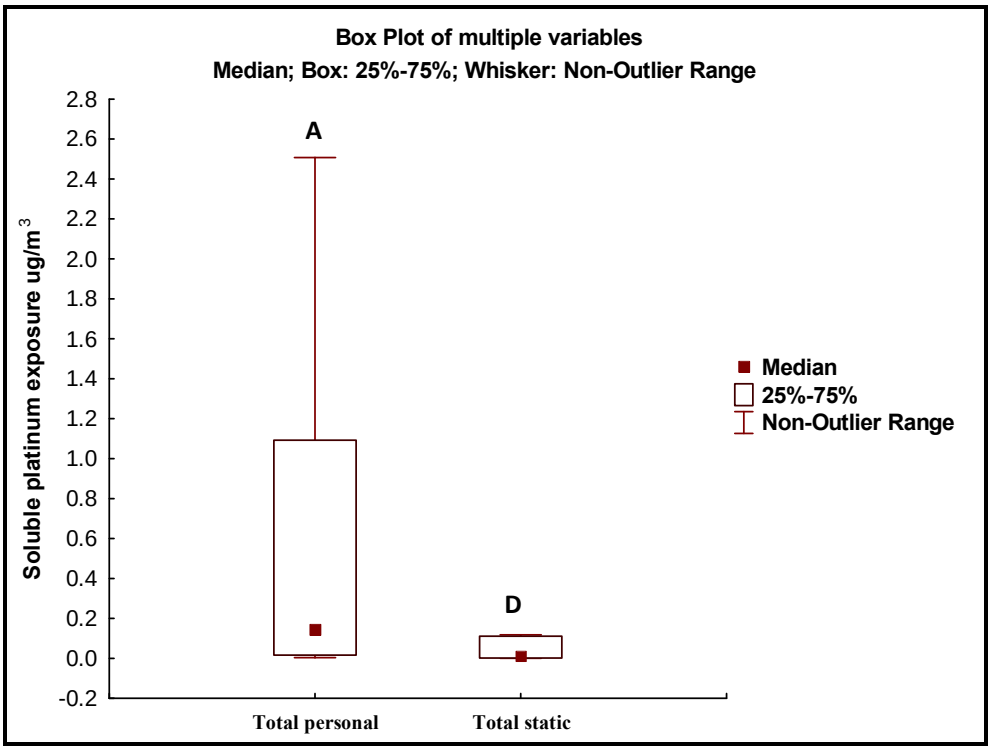


Fig. 3. Box and whisker plots plots illustrating (A) total personal and (D) total area platinum exposure

It is evident from Table 7 that there is a significant difference (p=0.004) between the total personal and total area exposure levels. The mean platinum exposure and distribution levels (personal and area) for each workarea are listed in Table 5 and 6 respectively and it can be noted that Bay 2 shows the highest personal exposure average (4.454 ± 8.489 µg/m$^3$) and Bay 5 the highest static exposure average (4.666 µg/m$^3$ ± 1.254 µg/m$^3$).

Table 5. Descriptive statistics for personal (production and engineering subgroups) and area (open and close face) exposure levels

| | Mean | Median | Min | Max including outliers | Max without outliers | Lower Quartile | Upper Quartile | SD |
|---|---|---|---|---|---|---|---|---|
| Personal exposure: total | 1.813 | 0.143 | 0.004 | 20.479 | 2.507 | 0.016 | 1.092 | 4.546 |
| Personal exposure: production | 2.739 | 0.736 | 0.010 | 20.479 | 5.544 | 0.031 | 2.507 | 5.644 |
| Personal exposure: engineering | 0.393 | 0.066 | 0.004 | 3.916 | 0.352 | 0.007 | 0.216 | 0.999 |
| Area exposure: total | 0.583 | 0.010 | 0.0004 | 5.752 | 0.118 | 0.002 | 0.111 | 1.475 |
| Area exposure: open face sampling | 0.725 | 0.013 | 0.0004 | 5.752 | 0.118 | 0.005 | 0.118 | 1.813 |
| Area exposure: closed face sampling | 0.441 | 0.008 | 0.0004 | 3.581 | 0.106 | 0.002 | 0.105 | 1.123 |

SD = standard deviation

Table 6. Descriptive statistics for soluble platinum exposure in each workarea

| Workarea | Exposure | Mean | Median | Min | Max include outliers | Max exclude outliers | Lower Quartile | Upper Quartile | SD |
|---|---|---|---|---|---|---|---|---|---|
| Bay 2 | p | 4.454 | 0.352 | 0.106 | 19.565 | 2.119 | 0.130 | 2.119 | 8.489 |
| Bay 3 | p | 3.671 | 0.971 | 0.156 | 20.479 | 3.732 | 0.279 | 3.120 | 6.906 |
| Bay 5 | p | 2.080 | 1,141 | 0.005 | 5.544 | 5.544 | 0.736 | 3.916 | 2.157 |
| Level 3 | p | 0.045 | 0.041 | 0.012 | 0.093 | 0.093 | 0.016 | 0.066 | 0.032 |
| Value recovery plant | p | 0.874 | 0.207 | 0.007 | 3.242 | 0.904 | 0.010 | 0.904 | 1.374 |
| Rhodium plant | p | 0.007 | 0.005 | 0.004 | 0.012 | 0.012 | 0.004 | 0.012 | 0.004 |
| Gold plant | p | 0.018 | 0.016 | 0.007 | 0.031 | 0.031 | 0.007 | 0.031 | 0.012 |
| Solvex plant[b] | p | 0.034 | 0.034 | 0.034 | 0.034 | 0.034 | 0.034 | 0.034 | - |
| SHE services[b] | p | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 | - |
| Bay 2 | s | 0.067 | 0.066 | 0.016 | 0.118 | 0.118 | 0.022 | 0.111 | 0.052 |
| Bay 3 | s | 0.341 | 0.015 | 0.004 | 1.317 | 1.317 | 0.005 | 0.689 | 0.550 |
| Bay 5 | s | 4.666 | 4.666 | 3.581 | 5.752 | 5.752 | 3.581 | 5.752 | 1.254 |
| Level 3 | s | 0.005 | 0.005 | 0.002 | 0.008 | 0.008 | 0.002 | 0.008 | 0.003 |
| Value recovery plant | s | 0.005 | 0.005 | 0.003 | 0.008 | 0.008 | 0.003 | 0.008 | 0.003 |
| Rhodium plant | s | 0.0005 | 0.001 | 0.0004 | 0.001 | 0.001 | 0.0004 | 0.001 | - |

p = personal exposure; s = area exposure; SD = standard deviation; b = indicates one measurement; SHE = safety health and environment;

Table 7. Mann-Whitney U test describing the statistical significance in exposure (marked tests are significant at p <0.05)

| Exposure µg/m$^3$ | Rank Sum | Rank Sum | U | Z | p-value | Z - adjusted | p-value | Valid N | Valid N | 2*1sided – p value |
|---|---|---|---|---|---|---|---|---|---|---|
| Personal | 520(pr) | 221(en) | 101 | 2.120 | 0.034 | 2.120 | 0.034 | 23 (pr) | 15 (en) | **0.033** |
| Area | 113(of) | 97(cf) | 42 | 0.567 | 0.571 | 0.567 | 0.571 | 10(of) | 10(cf) | **0.579** |
| Total | 1294(p) | 417(s) | 207 | 2.822 | 0.005 | 2.822 | 0.005 | 38(p) | 20(s) | **0.004** |

pr = production subgroup; en = engineering subgroup; of = open face exposure; cf = closed face exposure; p = personal exposure; s = area exposure

Figure 4 and 5 illustrate the distribution for personal and area exposure levels respectively in each workarea and it is evident from the Kruskal-Wallis test (Table 8) that there is a significant difference between the Rhodium plant and Bay 3 (p=0.041).

Table 8. Kruskal Wallis test describing the statistical significance in personal platinum exposure levels between different workareas (marked tests are significant at p <0.05)

Multiple Comparisons p values (2-tailed); **Personal exposure** (Spreadsheet area personal exp) Independent (grouping) variable: **Areas**
Kruskal-Wallis test: H ( 8, N= 38) =20.21564; **p = 0.0096**

| Areas | Bay 2 p value | Bay 3 p value | Bay 5 p value | Level 3 p value | RHD p value | VRP p value | AU Plant p value | SHEQ p value | Solvex p value |
|---|---|---|---|---|---|---|---|---|---|
| **Bay 2** | | 1.000 | 1.000 | 1.000 | 0.216 | 1.000 | 1.000 | 1.000 | 1.000 |
| **Bay 3** | 1.000 | | 1.000 | 0.382 | 0.041 | 1.000 | 0.416 | 1.000 | 1.000 |
| **Bay 5** | 1.000 | 1.000 | | 1.000 | 0.146 | 1.000 | 1.000 | 1.000 | 1.000 |
| **Level 3** | 1.000 | 0.382 | 1.000 | | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| **RHD** | 0.216 | 0.041 | 0.146 | 1.000 | | 1.000 | 1.000 | 1.000 | 1.000 |
| **VRP** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | | 1.000 | 1.000 | 1.000 |
| **AU Plant** | 1.000 | 0.416 | 1.000 | 1.000 | 1.000 | 1.000 | | 1.000 | 1.000 |
| **SHEQ** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | | 1.000 |
| **Solvex** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | |

RHD = Rhodium; VRP = Value Recovery Plant; AU = Gold; SHE = Safety, Health, Environment

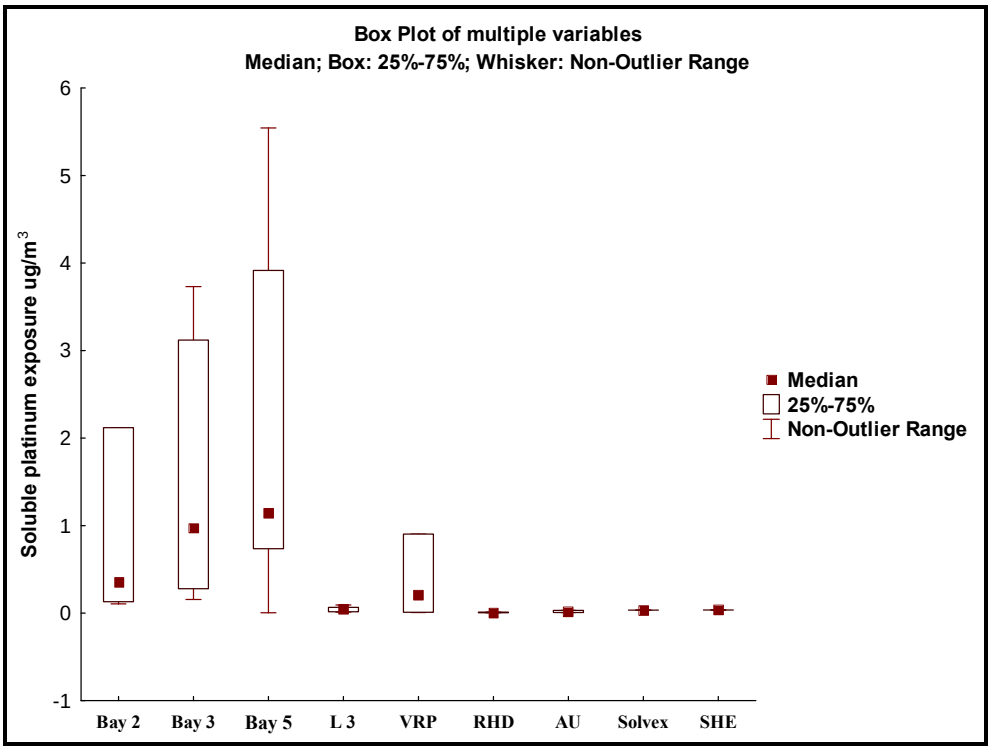


Fig. 4. Box and whisker plots illustrating personal platinum exposure for all areas.

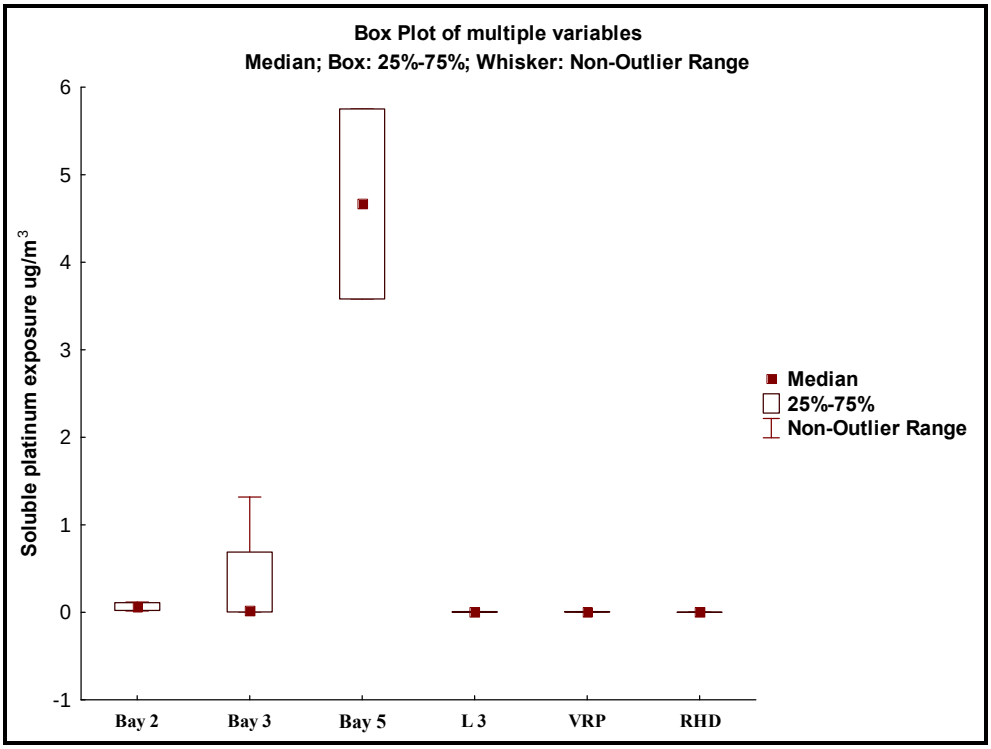


Fig. 5. Box and whisker plots illustrating area platinum exposure for all areas

**DISCUSSION**

It is evident from the results that the refinery workers were exposed to soluble platinum during the non-operational period while the refinery process was shut down for maintenance and stock take purposes and that 21% of the personal and 10% of the area measurements exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996). The personal platinum exposure concentrations ranged between 0.004-20.479 µg/m$^3$ and between 0.0004-5.752 µg/m$^3$ for area exposure.

Several studies reported refinery workers' platinum exposure levels to be between 0.01-80000 µg/m$^3$. Shi (1987) reported extremely high levels of platinum (5000-80000 µg/m$^3$) in a poorly ventilated platinum refinery in China with average platinum concentrations below 10000 µg/m$^3$ at most places measured. Fothergill *et al.* (1945) and Hunter *et al.* (1945) reported air levels of 0.9-1700 µg/m$^3$. The majority of the refining operations (wet processes and/or local exhaust ventilation), showed levels less than 5 µg/m$^3$. High levels of platinum (up to 1700 µg/m$^3$) were measured during the crushing of ammonium hexachloroplatinate(IV). Johnson *et al.* (1976) reported platinum air concentrations between 0.02-0.26 µg/m$^3$ (mean: 0.16 µg/m$^3$) in the refinery section and 0.13-0.21 µg/m$^3$ (mean: 0.18 µg/m$^3$) in the salts section.

Merget *et al.* (1988) reported platinum air levels below 0.08 µg/m$^3$, however, high exposure during the drying process of the salts was measured. Very low platinum air levels (<0.05 µg/m$^3$) were reported by Bolm-Audorff *et al.* (1992) and stationary air levels between 0.08-0.1 µg/m$^3$ were also reported. The HSE (1996) reported levels between 2-16 µg/m$^3$ and Maynard *et al.* (1997) stated levels between 0.01-26 µg/m$^3$.

The personal exposure results obtained during the study (0.004-20.479 µg/m$^3$) compared well with results reported by HSE (1996) and Maynard *et al.* (1997) although it must be noted that their studies were conducted during production. The sampled production subgroup displayed higher mean personal exposure levels (2.739 µg/m$^3$) compared to the sampled engineering subgroup (0.393 µg/m$^3$) and the difference was statistical significant (p=0.033). This was expected since the production workers were directly involved in the cleaning and flushing of plant equipment after it has been opened, posing a higher platinum exposure risk. The engineering workers were only involved in the dismantling of plant equipment after it has been flushed, limiting their exposure because of minimum contact with the residues and minimum time spent performing the task. Although the mean exposure levels for open face sampling were higher (0.725 µg/m$^3$) compared to the mean exposure levels for closed face sampling (0.441 µg/m$^3$) there was no significant difference (p=0.579) between the open and closed face sampling results.

The mean personal exposure levels were higher (1.813 µg/m$^3$) compared to the mean area exposure levels (0.583 µg/m$^3$) and differed significantly (p=0.004). This was expected since the employees sampled were working very close to the source of exposure and the further the location from the source the lower the level of exposure since air pollutants dilute in the air of the work area. Obtained results indicate that area monitoring is not an effective or accurate indicator of personal exposure levels since the average area exposure levels were much lower compared to the average personal exposure levels obtained. The task and workplace indicating the highest personal exposure concentration included the digging out of main draught line residues in Bay 3 (20.479 µg/m$^3$). This expected high exposure was the result of the worker being directly exposed to high amounts of concentrated residues when performing the task. Additional tasks indicating personal exposure levels that exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) included the following in descending order: cleaning of gloveboxes in Bay 2 (19.565 µg/m$^3$); cleaning of muffles in Bay 5 (5.544 µg/m$^3$); dismantling of muffles in Bay 5 (3.916 µg/m$^3$); digging out sump residues in Bay 3 (3.732 µg/m$^3$); cleaning dust extraction fan filters in the Value Recovery Plant (VRP) (3.242 µg/m$^3$); removal of module filters in Bay 3 (2.507 µg/m$^3$) and the scrubbing of tanks in Bay 2 (2.119 µg/m$^3$).

The workplace and task indicating the highest area exposure concentration included the cleaning of muffles in Bay 5 (5.752 µg/m$^3$). A second area exposure result that exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) also included the cleaning of muffles in Bay 5 (3.581 µg/m$^3$).

The following work areasô mean personal platinum exposure levels exceeded the OEL of 2 µg/m$^3$ (MHSA, 1996) in decreasing order: Bay 2 (4.454 µg/m$^3$), Bay 3 (3.671 µg/m$^3$) and Bay 5 (2.080 µg/m$^3$). Bay 5 was the only area where the mean area exposure level exceeded the OEL (4.666 µg/m$^3$). It is evident from the results that the platinum exposures were the highest in the Bays where most of the production of platinum salt takes place. This, in addition, is in line with the fact that platinum compounds are found in a soluble form (complex platinum salts) in the Bays. Most of the plant equipment including draught lines, tanks, gloveboxes, sumps, muffles and extraction fan filters are all contained in the Bays and hold concentrated platinum salt residues that pose a high platinum salt sensitising (PSS) risk when opened and cleaned during the non-operational period when measurements were taken.

## CONCLUSION

Platinum refinery workers were exposed to soluble platinum during the stock take period even to concentrations that exceeded the OEL. This was expected since the normally enclosed system were opened and cleaned, thus increasing the risk to be exposed to platinum salts and the development of PSS. The mean personal exposure levels for the production subgroup (2.739 µg/m$^3$) were significantly higher compared to the engineering subgroupôs mean personal exposure levels (0.393 µg/m$^3$). This significant difference (p=0.033) was expected since the production subgroup was more exposed and involved in the digging out of residues and the cleaning of plant equipment compared to the engineering subgroup with limited exposure and involved in the opening of plant equipment. Although the mean exposure levels for open face sampling (0.725 µg/m$^3$) were higher compared to the mean exposure levels for closed face sampling (0.441 µg/m$^3$) no significant difference (p=0.579) were noted. The mean area exposure levels (0.583 µg/m$^3$) were significantly lower (p=0.004) compared to the mean personal exposure levels (1.813 µg/m$^3$) for similar areas and tasks performed and therefore not an effective indicator of personal exposure levels. Higher personal exposure levels were expected since the workers were closer to the source of exposure and since the platinum salts could have diluted in the workplaceôs air, resulting in lower area exposure levels. Irrespective of the fact that 21% of the total personal exposure results exceeded the OEL of 2 µg/m$^3$ no platinum salt sensitisation cases were reported or diagnosed following the stock take period most probably as a result of a combination of factors including employees adhering to all recommended control measures (including engineering controls, administrative controls and personal protective equipment), highly qualified and competent employees and a significant reduction in the amount of plant equipment being dismantled during the 2010 stock take.

## REFERENCES

1. Baker DB, Gann PH, Brooks SM, Gallagher J, Bernstein IL. (1990) Cross-sectional study of platinum salts sensitization among precious metals refinery workers. Am J Ind Med; 18: 653-664.

2. Bolm-Audorff U, Bienfait HG, Burkhard J, Bury AH, Merget R, Pressel G, Schultze-Werninghaus G. (1992) Prevalence of respiratory allergy in a platinum refinery. Int Arch Occup Environ Health; 64: 257-260.

3. Bullock J. (2010) Chloroplatinate Toxicity: Use and Misunderstanding of Merget. International Precious Metals Institute. USA: Tucson, Arizona.

4. Fothergill SJR, Withers DF, Clements FS. (1945) Determination of traces of platinum and palladium in the atmosphere of a platinum refinery. Br J Ind Med; 2: 99-101.

5. Health and Safety Executive (HSE) (1996) Platinum metal and soluble platinum compounds in air: laboratory method using electrothermal atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. MDHS46/2. Sudbury (Suffolk), England: HSE Books, ISBN 0 7176 1306 2.

6. Health Council of the Netherlands. (2008) Platinum and platinum compounds. Health-based recommended occupational exposure limit. The Hague: HCN; publication no. 2008/12OSH. ISBN 978 90 5549 718 8.

7. Hunter D, Milton R, Perry KMA. (1945) Asthma caused by the complex salts of platinum. Br J Ind Med; 2: 92-98.

8. Johnson DE, Prevost RJ, Tillery JB, Caman DE, Hosenfeld JM. (1976) Baseline levels of platinum and palladium in human tissue. EPA/600/1-76/019. San Antonio, Texas: Southwest Research Institute. NTIS PB-251 885/0. pp. 252.

9. Liedel NA, Busch KA, Lynch JR. (1977) NIOSH: Occupational Exposure Sampling Strategy Manual (OESSM). U.S. Department of health, education and welfare public health service. Center for disease control. National institute for occupational safety and health. Washington D.C., U.S.: Government printing office.

10. Lindell B. (1997) DECOS and NEG Basis for an Occupational Standard. Platinum. Arbete och Hälsa; 14: 1-65. ISBN 9170454205.

11. Maynard AD, Northage C, Hemingway M, Bradley SD. (1997) Measurement of short-term exposure to airborne soluble platinum in the platinum industry. Ann Occup Hyg; 41(1): 77-94.

12. Merget R, Schultze-Werninghaus G, Muthorst T, Friedrich W, Meier J. (1988) Asthma due to the complex salts of platinum-a cross-sectional survey of workers in a platinum refinery. Clin Allergy; 18: 569-580.

13. Shi ZC. (1987) Platinosis. Proc ICMR Semin 1988 and Proc Asia-Pac Symp. Environ Occup Toxico; 1987: 133-135.

14. South Africa. (1996) Mine Health and Safety Act (MHSA), No. 26 of 1996. Pretoria: Government Printer. 2006 Occupational Exposure Limits For Airborne Pollutants.

15. World Health Organization (WHO). (2000) Inorganic pollutants: Platinum. In: Air quality guidelines for Europe. Copenhagen. WHO: 166-169.

# CHAPTER 4: GENERAL FINDINGS AND CONCLUSIONS

## 4.1 INTRODUCTION

In this final chapter, a summary of the main findings from the article (Chapter 3) will be given; conclusions will be drawn regarding the problem statement, objectives and hypotheses. A few improvements and points to consider are made regarding the control efficiency of existing control measures and recommendations for further studies are indicated.

## 4.2 PROBLEM STATEMENT

It was stated in the first chapter that no platinum exposure levels during non-operational periods were present for platinum refinery workers. The compliance and efficiency of control measures were also unknown. Through the literature study it became clear that platinum exposure studies were mostly done during production periods and has provided clear evidence that exposure to platinum salts during the refining process leads to occupational skin and respiratory hypersensitivity in humans; however, the extent of exposure during non-operational, non-routine stock take activities was unknown. Therefore, quantitative exposure measurements were carried out during this non operational period, quantified and conclusions were drawn following the interpretation of results.

## 4.3 SUMMARY OF THE MAIN FINDINGS

The general aim of this study was to measure occupational exposure of refinery workers to soluble platinum during non-operational periods. The specific aims were to: (i) quantify area and personal exposure levels during non-operational periods; (ii) identify work areas and work practices that result in exposure levels exceeding the occupational exposure limit (OEL) ($\geq$2 µg/m$^3$) during non-operational periods; determine whether the exposure levels differ significantly between the (iii) personal sampling groups (engineering versus production); (iv) area sampling groups (open versus closed-face sampling); (v) work areas and; (vi) between total area and total personal sampling groups to evaluate the effectiveness of area monitoring as a possible indicator of personal exposure levels and to; (vii) investigate the efficiency of the current control measures utilised. The study addressed the aims and the results indicate personal platinum exposure levels ranging from 0.004-20.479 µg/m$^3$ and area exposure levels ranging from 0.0004-5.752 µg/m$^3$. One fifth (21%) of personal exposure measurements and one tenth (10%) of area exposure measurements exceeded the OEL of 2 µg/m$^3$. The task and workplace indicating the highest personal exposure concentration included the digging out of main draught line residues in Bay 3 (20.479 µg/m$^3$).

Additional tasks indicating personal exposure levels that exceeded the OEL included the following in descending order: cleaning of gloveboxes in Bay 2 (19.565 µg/m$^3$); cleaning of muffles in Bay 5 (5.544 µg/m$^3$); dismantling of muffles in Bay 5 (3.916 µg/m$^3$); digging out sump residues in Bay 3 (3.732 µg/m$^3$); cleaning dust extraction fan filters in the Value Recovery Plant (VRP) (3.242 µg/m$^3$); removal of module filters in Bay 3 (2.507 µg/m$^3$) and the scrubbing of tanks in Bay 2 (2.119 µg/m$^3$). The workplace and task indicating the highest area exposure concentration (5.752 µg/m$^3$) included the cleaning of muffels in Bay 5. A second area exposure result that exceeded the OEL also included the cleaning of muffles in Bay 5 (3.581 µg/m$^3$). The following areasô average personal platinum exposure levels exceeded the OEL in decreasing order: Bay 2 (4.454 µg/m$^3$), Bay 3 (3.671 µg/m$^3$) and Bay 5 (2.080 µg/m$^3$). Bay 5 was the only area where the average static exposure level exceeded the OEL (4.666 µg/m$^3$).

It was hypothesised that:

a) refinery workers are exposed to airborne soluble platinum during non-operational periods;
b) exposure levels do not differ significantly between the personal sampling groups (engineering versus production);
c) exposure levels do not differ significantly between the area sampling groups (open versus closed face sampling);
d) exposure levels do not differ significantly between work areas;
e) exposure levels differ significantly between total personal and total area sampling groups.

The results confirmed that refinery workers are exposed to airborne soluble platinum during non-operational periods and hypothesis a was accepted. Inter-personal exposure levels (engineering versus production) differed statistically (p=0.033) and hypothesis b was rejected. The inter-area exposure levels (open face versus closed face) indicated no statistical difference (p=0.579) and hypothesis c was accepted. In addition the inter-workarea exposure levels also did not differ statistically (p>0.05) and hypothesis d was accepted. Total personal versus total area exposure levels (p=0.004) differed statistically and hypothesis e was accepted.

### 4.4 REQUIRED EXPOSURE CONTROLS

ACGIH (1990) and HSE (1996) states that personal exposure to soluble platinum should be kept below 2 µg/m$^3$ for an 8-hour time-weighted average total inhalable dust. This level or greater dust concentrations should be regarded as substantial concentrations. Not all dusts have been designated occupational exposure limits but the lack of such limits should not be considered an absence of hazard. In the absence of a specific exposure limit for a particular substance, exposure should be adequately controlled.

In fact, if a hazardous agent is found to be present in the workplace in concentrations that could cause health effects, it must be controlled. Control means eliminating the hazard or reducing it to a level that protects workers from adverse health effects. Hazards may be controlled at the source, along the path from the source to the worker, or at the worker.

To be effective, a control measure must satisfy the following criteria:

a) adequately control the hazard to eliminate the danger to the worker;
b) protect all workers who are likely to be exposed;
c) must not create a new hazard in the workplace or
d) an environmental hazard outside the workplace.

The Mine Health and Safety Act (1996) requires an occupational hygiene programme of all working places where the TWA concentration of airborne pollutants exceeds or equals a tenth of the occupational exposure limit. This must be periodically reviewed to determine whether additional elimination, control and minimisation of risk are possible. Records must be kept of the measurements, management and medical examination of these airborne pollutants. The Hazardous Chemical Substances Regulations (1995) require that an employee must be trained and informed regarding potential source exposures, potential risks to health caused by exposure and the measures to be taken by the employers and workers to protect the workers against health risks associated with such exposure, including the wearing and use of protective clothing and respiratory protective equipment. Furthermore, periodical medical surveillance (chest x-ray and spirometry) must be done when the exposure of the employee to any hazardous substance is such that an identifiable disease or adverse effect may be related to the exposure. When there is no other way of prevention or managing of exposure, appropriate PPE must be provided.

## 4.5 EXISTING CONTROL MEASURES

Control measures currently in place to control exposure to soluble platinum salts effectively.

### 4.5.1 Engineering controls:

1. Enclosed system (Total enclosure of process)
2. Supply and extraction ventilation systems in all production areas
3. Draught system on process equipment
4. Automated process operation.

### 4.5.2 Administrative control measures:

1. Occupational Hygiene monitoring programmes
2. Reduction of exposure time (work-rest cycles, shift arrangements)
3. Provision of hygiene facilities (wash facilities, clean and dirty change houses, laundry and canteens)
4. Safe work procedures and systems
5. Training on and awareness of PSS
6. Utilisation of sodium borohydride (reduces the salt to a metal, rendering it non-sensitising)
7. Medical surveillance (initial medical, routine medicals, annual medical and exit medical)
   The workers undergo an annual chest x-ray and a spirometry test to assess the health of their lungs, which forms part of the medical surveillance. The chest x-ray is taken to look for lung damage (darkened or white spots). The spirometry test includes forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC expressed as a percentage. This annual spirometric test is compared to the baseline spirometric test. Clinical evaluation is required when a decline in lung volume occur, an exceeded average of 200 mL between tests. In addition skin prick tests are done every third month and are a reliable way of determining whether a person has been sensitised or not.
8. Effective planning and supervision
9. Highly qualified and competent employees
10. Safety first culture and zero harm approach
11. Highest level of housekeeping.

### 4.5.3 Personal Protective Equipment (PPE):

1. Long sleeve khaki clothes
2. Rubber gloves
3. Chemical resistant safety glasses and boots
4. Disposable overalls
5. Respiratory protection (Half or full face masks, airstream helmets and airlines).

## 4.6 EFFICIENCY OF EXISTING CONTROL MEASURES

The refinery did comply with all the legislative control measures and the high exposure levels documented during this non-operational period were not because of ineffective control measures but because some of the existing control measures (such as the enclosed process, draught system and automated process operation) were compromised during the shutdown during which the enclosed system was opened, the draught system was offline and the equipment was dismantled and cleaned manually.

However, where reasonably practicable, the control measures that could be applied were in place and efficient and none of the workers exposed to platinum levels above the OEL during this non-operational period experienced any PSS symptoms.

Recommendations and improvements regarding current controls included the following:

a) No respiratory fit testing programme was in place. The company should consider this fit testing, combining it into the annual medical surveillance of the worker. Consider the taste test for the specific mask the workers are wearing in order to be sure that the worker is effectively protected against the dust. During the medical surveillance, the worker can be refreshed on the proper donning and doffing of the mask he/she is wearing, how to check if it fits properly, maintenance of the mask and positive and negative properties of the mask.
b) Training on the correct selection and proper use of respirators, i.e. respirators must be selected by means of a respirator fit test, the substance and the concentrations to which the worker is exposed to and the function of such a specific respirator. Proper use of PPE is insured when the worker understands his liability towards wearing the PPE, know how to maintain his/her PPE and when to replace his/her PPE, combined with necessary supervision with regard to the use of the equipment. Wrong respirators were sometimes resourced that would not effectively protect the worker against the hazard.
c) It must be ensured that workers remove and dispose dirty or contaminated personal protective equipment in the correct manner in particular contaminated gloves that were not always removed in the correct manner from the hands and could cause contamination of the skin and serious adverse health effects.

## 4.7 RECOMMENDATIONS FOR FURTHER STUDIES

During the writing of this dissertation, a few gaps and needs for further studies were identified and are presented below:

a) No respirable measurements were taken. This was due to financial restrictions from the source financial provider, which only budgeted for inhalable dust measurements and analysis. In future studies a budget for respirable measurements should be considered.
b) It is suggested doing a study on platinum speciation, focusing on the specific type of platinum salt produced in that area
c) An occupational health study that include personal, dermal and biological monitoring of soluble platinum at the same time to determine if there is a correlation between personal dermal and systemic exposure levels.

d) In addition, current analytical methods do not distinguish between halogeno-platinates and other soluble platinum compounds. Consequently new analytical methods are required to establish the speciation of platinum in the environment given that not all platinum species elicit sensitisation.

e) Data on reproduction toxicology, genotoxicity, and carcinogenicity is very limited and further studies are recommended in these fields.

## 4.8 CONCLUSION

Platinum refinery workers were exposed to soluble platinum during the stock take period even to concentrations that exceeded the OEL. This was anticipated since the normally enclosed system were opened and cleaned, thus increasing the risk to be exposed to platinum salts and to develop PSS. The exposure levels were very high for the production subgroup that was involved in the digging out of residues and the cleaning of plant equipment compared to the engineering subgroup involved in the opening of plant equipment. Area exposure levels were much lower compared to the personal exposure levels for similar areas and tasks performed and therefore not an effective indicator of personal exposure levels. Higher personal exposure levels were projected since the workers were closer to the source of exposure and since the platinum salts could have diluted in the workplace's air, resulting in lower area exposure levels. Irrespective of the fact that 21% of the total personal exposure results exceeded the OEL of 2 $\mu g/m^3$ no PSS cases were reported or diagnosed following the stock take period most probably as a result of a combination of factors including employees adhering to all recommended control measures (including engineering controls, administrative controls and personal protective equipment), highly qualified and competent employees and a significant reduction in the amount of plant equipment being dismantled during the 2010 stock take. The study met the points set out in chapter one, hypotheses were rejected and accepted, recommendations were made on current control measures and future studies were suggested.

## 4.9 REFERENCES

1. American Conference of Industrial Hygienists (ACGIH). (1990) Threshold limit values for chemical substances and physical agents and biological exposure indices for 1990-1991. Cincinnati, OH, American Conference of Governmental Industrial Hygienists.

2. Health and Safety Executive (HSE) (1996) Platinum metal and soluble platinum compounds in air: laboratory method using electrothermal atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. MDHS46/2. Sudbury (Suffolk), England: HSE Books, ISBN 0 7176 1306 2.

3. South Africa. (1995) Hazardous Chemical Substances Regulations (HCSR), Regulation 1779 of 25. August, 1995. Pretoria: Government Printer.

4. South Africa. (1996) Mine Health and Safety Act (MHSA), No. 26 of 1996. Pretoria: Government Printer.

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

## ANNEXURE A: GRAVIMETRIC FIELD SHEET

AngloAmerican

**PLATINUM**
**PMR-SHEQ-OCH-PRO-0004-FRM-00**
**REV 3.0**

| IRM.net sample ID: | | | | | | Sample type: | Scheduled | Special / Project | Shutdown |
|---|---|---|---|---|---|---|---|---|---|

**ACKNOWLEDGEMENT OF PERSONAL SAMPLER WEARER RESPONSIBILITIES AND PARTIAL SUPERVISOR REPORT IN TERMS OF PMR GRAVIMETRIC SAMPLING STRATEGY**

1. Personal samplers are issued to wearers as a legal requirement in terms of the Mine Health and Safety Act, Act 29 of 1996.
2. The sampler will be worn at all times for the duration of working shift
   This time includes periods spent in the canteen and toilets.
3. The sampler will be worn at all times in the manner described by the issuing Officer/ Occupational Hygiene Assistant.
4. When disposable overalls or other protective clothing is required to be worn, it shall be worn under the filter paper cassette.
5. Under no circumstances must the sampler pump unit be tampered with.
6. The wearer must take every precaution to ensure that the filter cassette holder and the tubing connecting it to the pump unit, is not damaged in use.

I, the undersigned, acknowledge that I have read and have understood the aforementioned points and hereby accept my responsibility as a wearer.

| Date: | | Employee: | | Coy #ò | |
|---|---|---|---|---|---|
| Job title: | | | | Signature: | |

| Areas worked | Duties performed |
|---|---|
| | |

Partial supervision is accomplished by adequate inspections of instruments at random by the supervisor to ensure as far as practical, that an accurate assessment of worker exposure is achieved.

| Supervisor: | | Signature: | |
|---|---|---|---|

| Occupation of issuer: | | Signature: | |
|---|---|---|---|
| Point of issue / return: | | Start time: | Finish time: |
| Condition of sampling train: | | Before:<br>After: | Good / Bad<br>Good / Bad |

SAMPLER # _____ FILTER # _____

## ANNEXURE B: GRAVIMETRIC CALIBRATION CONTROL SHEET

AngloAmerican

**GRAVIMETRIC CALIBRATION CONTROL SHEET**

**PLATINUM**
**PMR-SHEQ-OCH-PRO-0011-FRM-001**
**REV 1.0**

| Date | Pump number | Filter number | Calibration before (L/min) | Signature | Calibration after (L/min) | Signature | Area sampled | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

## ANNEXURE C: FIGURES

Figure C1. Bay 3 ï Digging out main draught line residues (20.479 ε g/m$^3$)


Figure C2. Bay 2 ï Cleaning gloveboxes (19.565 ε g/m$^3$)


Figure C3. Bay 5 - Dismantling (3.916 ε g/m$^3$) and cleaning (5.544 ε g/m$^3$) muffles

Figure C4. Bay 3 ï Digging out sump residues (3.732 ε g/m$^3$)

## ANNEXURE C: FIGURES (CONTINUED)

Figure C5. VRP ï Cleaning dust extraction fan filters (3.242 ε g/m$^3$)

Figure C6. Bay 3 ï Removing module filters (2.507 ε g/m$^3$)

Figure C7. Bay 2 ï Scrubbing tanks (2.119 ε g/m$^3$)