Platinum and platinum compounds

Health-based recommended occupational exposure limit

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

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Geachte minister,

Graag bied ik u hierbij het advies aan over de beroepsmatige blootstelling aan platina en platinaverbindingen. Het maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige advieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Dit advies over platina en platinaverbindingen is opgesteld door de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en aan de minister van Ruimte en Milieu.

Hoogachtend,

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Platium and platinum compounds

Health-based recommended occupational exposure limit

to:

the Minister of Health, Welfare and Sport

No. 2008/12OSH, The Hague, June 12, 2008

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Contents

10 Platinum and platinum compounds

Samenvatting en advieswaarde

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS, voorheen WGD) van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in lucht op de werkplek waaraan mensen beroepsmatig kunnen worden blootgesteld. In dit advies worden het metaal platina en een aantal platinaverbindingen onder de loep genomen.

Het advies is opgesteld in samenwerking met de Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), een adviescommissie van de Noord-Europese regeringen. Het gezamenlijke rapport over de gevolgen van beroepsmatige blootstelling aan platina en platinaverbindingen, gepubliceerd in Zweden in 1997 (Arbete och Hälsa 1997: 14), is in zijn geheel opgenomen in deel 2 van dit advies. Deel 1 bestaat uit een kort overzicht van de onderzoeken die in deel 2 aan de orde komen, een bespreking van de onderzoeksgegevens die sinds 1997 beschikbaar zijn gekomen, en de gezondheidskundige evaluatie van platina en zijn verbindingen.

De conclusies in het advies zijn gebaseerd op wetenschappelijke publicaties die vóór september 2007 zijn verschenen. Ze komen geheel voor rekening van de commissie GBBS van de Gezondheidsraad.

Fysische en chemische eigenschappen en gebruik

In het rapport worden platina (CAS nummer 7440-06-4) en een aantal platinaverbindingen behandeld. Op platina gebaseerde geneesmiddelen tegen kanker (zoals bij voorbeeld cisplatina) worden niet besproken.

Platina is een zilvergrijs edelmetaal. Het wordt verkregen door winning uit ertsen of door recycling van platinahoudende metalen, en gezuiverd door omzetting in hexachloroplatinazuur. Platina is van grote commerciële waarde, omdat het in hoge mate bestand is tegen corrosie. Ook is het waardevol als katalysator voor oxidatie- en reductieprocessen.

Platina en zijn verbindingen worden hoofdzakelijk gebruikt in de automobielindustrie (als katalysator in de uitlaat van auto's). Daarnaast wordt het toegepast in sieraden en elektronica en in de (petro)chemische industrie en, in nog geringere mate, in de tandheelkunde (voor bruggen, kronen, en dergelijke). Ook wordt platina gebruikt in de farmaceutische industrie (in geneesmiddelen tegen bepaalde vormen van kanker).

Monitoring

Blootstelling aan platina en platinaverbindingen vindt voornamelijk plaats door inademing van stofdeeltjes. Om concentraties van platina en platinaverbindingen op de arbeidsplek te kunnen meten, zijn methoden ontwikkeld om de concentraties in de lucht te kunnen bepalen.

Verschillende organisaties, zoals het Engelse Health and Safety Executive (HSE) en het Amerikaanse National Institute for Occupational Safety and Health (NIOSH) en de Occupational Safety and Health Administration (OSHA), hebben manieren beschreven om dat te doen.

De lucht wordt dan aangezogen via filters, waarna de filters worden behandeld met een zure oplossing. Met behulp van speciale spectrometrische technieken wordt vervolgens de hoeveelheid platina bepaald. In het algemeen zijn langdurige monsternemingen nodig. De bepalingsmethoden kunnen geen onderscheid maken tussen metallisch platina en platinaverbindingen.

NIOSH heeft ook methoden beschreven voor de bepaling van platina in biologische monsters (bloed, weefsel, urine).

Huidige grenswaarden

In Nederland geldt een wettelijke grenswaarde voor beroepsmatige blootstelling aan deeltjes metallisch platina van 1 mg platina per m^3 lucht. Deze waarde is in overeenstemming met Europese richtlijnen. Nederland heeft geen waarde(n) voor platinaverbindingen. Een aantal Europese landen (Denemarken, Engeland, Finland, Noorwegen, Zweden) en Amerikaanse organisaties (ACGIH, NIOSH, OSHA) hanteren grenswaarden voor platinazouten die oplosbaar zijn in water van 2 µg platina per m^3 lucht.

Kinetiek

Platinadeeltjes en platinazouten die het lichaam binnenkomen via de ademhalingsorganen en de mond worden niet gemakkelijk opgenomen, tenminste als ze niet in water oplosbaar zijn. De absorptie is in dat geval waarschijnlijk minder dan 1%. Platinazouten die wel oplossen in water worden echter beter geabsorbeerd.

Platina dat in het lichaam wordt opgenomen wordt verdeeld over de ‘zachte’ weefsels, met name de nieren, maar wordt soms ook teruggevonden in het botstelsel. De uitscheiding vindt voornamelijk met de urine plaats en lijkt zich in twee fasen te voltrekken. Bij mensen zijn twee biologische halfwaardetijden vastgesteld van respectievelijk ongeveer 50 uur en ongeveer 24 dagen. In de literatuur zijn geen gegevens te vinden over de omzetting in het lichaam van platina of platinaverbindingen.

Effecten op mensen

Platina en platinaverbindingen die niet oplosbaar zijn in water

Er zijn geen gegevens beschikbaar uit onderzoek naar de mogelijke effecten bij mensen door blootstelling aan metallisch platina en niet-oplosbare platinaverbindingen.

In water oplosbare platinaverbindingen

Over de effecten van oplosbare platinaverbindingen zijn wel gegevens beschikbaar. Daaruit blijkt dat contact met deze verbindingen vooral leidt tot overgevoeligheid en allergische aandoeningen van de ademhalingsorganen en de huid. Met

name geladen complexen bestaande uit platina en halogeengroepen leidden tot dit type klachten. Bij ongeladen platinacomplexen en complexen die andere groepen dan halogenen als ligand hebben kwamen deze klachten daarentegen niet voor.

In een prospectieve cohortstudie, uitgevoerd door Merget et al., is een dosis-effectrelatie gevonden tussen de concentraties van in de lucht aanwezige oplosbare platinazouten, platinaconcentraties in het serum van blootgestelde werknemers en het optreden van nieuwe gevallen van overgevoeligheid in die werknemers. Het onderzoek werd uitgevoerd in de periode van 1989 tot 1995 en omvatte in totaal 275 werknemers van een Duitse katalysatorfabriek. In 1992 en 1993 werden oplosbare platinaten in de lucht gemeten, met monsterperioden van 12-17 uur. In 1993 werden persoonsgebonden monsternemingen (met een duur van ongeveer 8 uur) uitgevoerd bij personen die blootgesteld waren aan hoge concentraties platinaten. In de groepen die werkten in ruimten waar geen of slechts in geringe mate blootstelling aan platinaten plaatsvond, traden gedurende de vijf jaar die de studie besloeg geen nieuwe gevallen van sensibilisatie op. De mediane concentraties in deze ruimten varieerden van 6,6 (1992) tot 0,4 (1993) ng platina per m^3. In de groep van 115 werkers die waren blootgesteld aan hoge concentraties platinaten, werden veertien nieuwe gevallen van sensibilisatie geconstateerd. De mediane concentraties varieerden van 14 tot 37 ng platina per m^3. Persoonsgebonden monsterneming resulteerde in een mediane blootstellingswaarde van 177 ng/m^3, met een hoogste waarde van 3700 ng/m^3; 3 van de 22 metingen overschreden de grenswaarde van 2000 ng/m^3. Het roken van sigaretten bevorderde het ontstaan van overgevoeligheidsreacties.

In een retrospectief onderzoek van Linnett en Hughes werden geen overgevoeligheidsreacties gevonden bij een groep werkers die gedurende vele jaren was blootgesteld aan tetraammineplatinadichloride. De concentraties waren meestal lager dan 0,5 µg platina per m^3, al werden soms concentraties hoger dan 2 of 10 µg platina per m^3 gemeten.

Effecten op proefdieren

In het algemeen blijken de schadelijke effecten van platina(verbindingen) na eenmalige toediening aan proefdieren gering. De mate waarin effecten optreden is afhankelijk van de oplosbaarheid in water: de onoplosbare zouten (en het metaal) zijn minder schadelijk en irriterend dan de oplosbare zouten.

Platina en platinaverbindingen die niet oplosbaar zijn in water

Er zijn geen gegevens beschikbaar uit dierexperimenteel onderzoek naar de oogirriterende of sensibiliserende eigenschappen van platina en niet-oplosbare platinaverbindingen. Platinadioxide en platinadichloride veroorzaakten geen irritatie van de huid.

Er is geen onderzoek beschikbaar waarin proefdieren eenmalig of herhaaldelijk via de ademhalingswegen zijn blootgesteld aan platina of niet-oplosbare platinaverbindingen. In een studie waarin ratten dagelijks gedurende 4 weken 700 mg platina per kilogram lichaamsgewicht in het voer kregen toegediend, werden geen effecten gezien.

Effecten op het erfelijk materiaal zijn alleen in enkele testen met platinadichloride onderzocht. De stof bleek niet mutageen in een cellijn van dierlijke oorsprong en veroorzaakte geen andersoortige schade aan het DNA van bacteriën of van cellen van menselijke oorsprong. Micronucleustesten in een humane cellijn lieten zowel positieve als negatieve resultaten zien. In de positieve test was sprake van zowel structurele als numerieke chromosoomafwijkingen. Onderzoek naar kanker ontbreekt.

In onderzoek naar eventuele schade op de voortplanting werden geen effecten gezien op het nageslacht van ratten die dagelijks 0,1 tot 100 mg platina per kilogram voer als metallisch platina kregen toegediend vóór en tijdens de dracht. Dagelijkse toediening aan ratten van 0,1 tot 100 mg platina per kilogram voer als platinadichloride tijdens de zoogperiode had ook geen effect op de nakomelingen.

In water oplosbare platinaverbindingen

Dierexperimenteel onderzoek geeft aan dat oplosbare platinaverbindingen huidirritatie en ernstig oogletsel kunnen veroorzaken. Onderzoek met muizen bevestigde de sensibiliserende eigenschappen van chloroplatinacomplexen en de afwezigheid daarvan voor een andere verbinding: tetraammineplatinadichloride.

Er is geen onderzoek beschikbaar waarin proefdieren eenmalig of herhaaldelijk via de ademhalingswegen zijn blootgesteld aan oplosbare platinaverbindingen. Bij eenmalige toediening van chloroplatinaverbindingen via de mond lagen de hoeveelheden die sterfte veroorzaken bij 50% van de blootgestelde groep (LD_{50}) tussen de 10 en 100 mg platina per kilo lichaamsgewicht. Bij hoeveelheden van 50 mg platina per kilogram lichaamgewicht, toegediend in de vorm van verschillende oplosbare platinazouten in het drinkwater, gedurende 4

weken, vertoonden ratten naast een afname van het lichaamsgewicht vooral effecten op de nieren. In sommige van deze onderzoeken veroorzaakten doseringen van 10 mg platina veranderingen in het bloedbeeld.

Om na te gaan of blootstelling tot schade aan het erfelijk materiaal kan leiden, werden met verschillende zouten testen uitgevoerd die mutaties of andersoortige veranderingen in het DNA of in chromosomen kunnen aantonen. In deze tests werden zowel positieve als negatieve resultaten verkregen.

Of in proefdieren schade aan het erfelijk materiaal kan ontstaan, is onderzocht door twee verschillende oplosbare platinacomplexen via de mond toe te dienen. Beide complexen waren na eenmalige orale toediening negatief in een micronucleustest in rode bloedcellen van muizen. Evenmin werden na herhaalde orale toediening veranderingen gezien in de chromosoomstructuur in beenmergcellen van hamsters. Onderzoek naar kanker ontbreekt.

In onderzoek naar eventuele schade op de voortplanting werden geen effecten gezien op het nageslacht van ratten die dagelijks 0,1 tot 100 mg platina per kilogram voer als platinatetrachloride kregen toegediend vóór en tijdens de dracht of tijdens de zoogperiode.

Evaluatie en advies

Platina en platinaverbindingen die niet oplosbaar zijn in water

Op basis van de beschikbare gegevens kan de commissie geen oordeel vellen over de schade die blootstelling aan platina en onoplosbare platinaverbindingen eventueel kan veroorzaken aan het erfelijk materiaal, het nageslacht of de voortplantingsorganen.

Naar het oordeel van de commissie zijn de beschikbare toxicologische gegevens uit humaan en dierexperimenteel onderzoek evenmin toereikend voor het afleiden van een gezondheidskundige advieswaarde voor beroepsmatige blootstelling aan platina en niet-oplosbare platinaverbindingen.

In water oplosbare platinaverbindingen

Ook over de schade die blootstelling aan oplosbare platinaverbindingen eventueel kan veroorzaken aan het erfelijk materiaal, het nageslacht of de voortplantingsorganen, kan de commissie geen oordeel vellen, omdat de beschikbare gegevens niet toereikend zijn.

Wel is een oordeel mogelijk over de relatie met overgevoeligheid en allergische aandoeningen. De beschikbare toxicologische gegevens uit humaan en dierexperimenteel onderzoek wijzen erop dat een bepaald type verbinding, namelijk de oplosbare (geladen) chloroplatinaten, overgevoeligheid en allergische aandoeningen van de ademhalingsorganen en de huid kan veroorzaken. Dit in tegenstelling tot ongeladen platinacomplexen en complexen die andere groepen dan halogenen als ligand hebben.

De commissie concludeert op grond van de studie van Merget dat er voor overgevoeligheidsreacties door blootstelling aan chloroplatinaten een drempelwaarde bestaat waaronder geen effecten te verwachten zijn. Zij acht het niet waarschijnlijk dat klachten zullen ontstaan als gevolg van blootstelling aan concentraties van 10 ng platina per m^3 en lager.

Daarom heeft de commissie deze concentratie als uitgangspunt genomen voor de afleiding van een gezondheidskundige advieswaarde. Omdat de onderzochte groep werkers relatief klein is (n=115), past de commissie een extrapolatiefactor van 2 toe. Uitgaande van het 'niet-nadelig-effect'-niveau van 10 ng platina per m^3 en een extrapolatiefactor van 2, stelt de commissie een gezondheidskundige limietwaarde voor van 5 ng platina per m^3, gemiddeld over een achturige werkdag. De limietwaarde geldt alleen voor oplosbare chloroplatinaten.

Gezondheidskundige advieswaarde

De commissie GBBS van de Gezondheidsraad beveelt voor één type, in water oplosbare platinaverbindingen, namelijk chloroplatinaten, een gezondheidskundige advieswaarde aan van 5 ng platina per m^3, gemiddeld over een achturige werkdag.

Bij gebrek aan geschikte gegevens kan de commissie geen voorstel doen voor een gezondheidskundige advieswaarde voor platina en platinaverbindingen die niet oplosbaar zijn in water.

Wel meent de commissie dat de resultaten van de studie van Linnett en Hughes aanleiding geven te veronderstellen dat van tetraammineplatinadichloride geen schadelijke gezondheidseffecten te verwachten zijn bij blootstellingsconcentraties van 0,5 µg platina per m^3.

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in the air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS).

The present advice on platinum and platinum compounds was prepared in cooperation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG), an advisory body of the Nordic countries. The joint report on the consequences of occupational exposure to platinum and platinum compounds, published in Sweden in 1997 (Arbete och Hälsa 1997:14) is included in Part II of this document. Part I consists of a summary of the data presented in Part II, presentation of data becoming available since 1997, and a discussion of the consequences of occupational exposure to platinum and its compounds. The conclusions in this advice are based on scientific publications which appeared before September 2007, and are entirely DECOS' view.

Physical and chemical characteristics and use

The report covers metallic platinum (CAS number 7440-06-4) and a number of platinum compounds. Platinum-based drugs (particularly cytostatics/chemotherapeutics like e.g., cisplatin) are not covered.

Platinum is a silver-grey noble metal of high commercial value due to its resistance to corrosive agents and its properties as an oxidation and reduction catalyst. It is obtained from mined ore and recycled metal; refining is done by conversion to hexachloroplatinic acid.

Platinum and its salts are mainly used in the automotive industry (as catalysts in motor car exhausts). It is further used in jewellery, electronics, and (petro)chemical industry, and, in even smaller amounts, in dentistry (bridges, crowns) and in medicine (anti-cancer drugs).

Monitoring

Several organisations, such as the UK Health and Safety Executive (HSE) and the US National Institute for Occupational Safety and Health (NIOSH) and Occupational Safety and Health Administration (OSHA), have described methods that can be used for analysing platinum and platinum compounds in workplace air. Air is filtered. Loaded filters are treated with acid solutions, and the extracts are analysed by specific spectrometric techniques. Generally, lengthy sampling times are required. The methods cannot distinguish between platinum and platinum compounds.

NIOSH has also described methods for analysing platinum in biological samples (blood, tissue, urine).

Limit values

In the Netherlands, there is a legally binding limit for metallic platinum of 1 mg Pt/m^3 of air, in line with European Commission directives. There are no limit values for platinum compounds. A number of European countries (Denmark, England, Finland, Norway, Sweden) and US organisations (ACGIH, NIOSH, OSHA) have occupational exposure limits for water-soluble platinum compounds of 2 µg Pt/m^3.

Kinetics

Inhalation and oral absorption of platinum metal and the water-insoluble platinum compounds is very low (probably less than 1%). Water-soluble platinum compounds are absorbed to a somewhat higher degree.

Absorbed platinum is distributed to the soft tissues and sometimes also found in the bones. Excretion of bioavailable platinum appears to occur via a biphasic process, mainly in the urine; in humans, the two half lives were ca. 50 hours and ca. 24 days, respectively. Data on biotransformation of platinum or its salts were not found.

Effects in humans

Platinum and water-insoluble platinum compounds

No data are available on the effects on humans following exposure to platinum and insoluble platinum compounds.

Water-soluble compounds

Human data indicate that the most significant risks from occupational exposure to soluble compounds are respiratory sensitisation and skin effects. Especially charged complexes with a halide ligand coordinated to platinum provoked these reactions, while uncharged complexes and soluble complexes in which the halide is present as an ion did not.

In a 5-year prospective cohort study, Merget and co-workers showed a dose-response relationship between airborne soluble platinum-compound concentrations, platinum concentrations in sera of exposed workers, and newly occurring sensitisations. The study was performed in the period 1989-1995, and included a total of 275 employees of a German catalyst-production plant. Water-soluble airborne platinum concentrations were measured in 1992 and 1993, with sampling periods of 12-17 hours. Personal sampling (duration about 8 hours) was performed in 1993 in highly exposed subjects. During the 5-year study period, no new sensitisations occurred in the workers with the no or low exposure. The median concentrations in the ‘low-exposure’ area were 6.6 and 0.4 ng Pt/m^3 in 1992 and 1993, respectively. In the group of 115 highly exposed workers, 14 new sensitisations occurred. The median concentrations in the ‘high-exposure’ area ranged from 14 to 37 ng Pt/m^3. Personal sampling in the highly exposed workers

revealed a median value of 177 ng/m^3 with a highest value of 3700 ng/m^3. Three measurements (out of 22) exceeded the current threshold limit value of 2000 ng/m^3. Smoking cigarettes was positively associated with the development of some work-related allergies.

In a retrospective study of Linnett and Hughes, no allergic reactions were observed in workers occupationally exposed to levels of tetraammineplatinum dichloride mostly below 0.5 µg/m^3 but occasionally higher than 2 or 10 µg/m^3.

Effects in experimental animals

Generally, the acute toxicity of platinum (compounds) is low and depends on their water solubility: the insoluble salts are less toxic or irritating than the soluble ones.

Platinum and water-insoluble platinum compounds

No experimental animal data are available on the potential eye-irritating or sensitising properties of platinum or insoluble platinum compounds. Platinum dioxide and platinum dichloride were not irritating to the skin.

No data were available from experimental animal inhalation studies. No effects were seen in rats given daily amounts of platinum in the diet of 700 mg/kg bw for four weeks.

For the only insoluble platinum compound tested, viz., platinum dichloride, *in vitro* tests for mutations (mouse lymphoma L5178Y cells) and DNA damage in bacteria (*E. coli*: SOS chromotest) and mammalian cells (human lymphocytes: comet assay) were negative. Both positive and negative results were reported in micronucleus tests in human lymphocytes. The induction of micronuclei was due both to clastogenic and aneuploidogenic mechanisms. Carcinogenicity studies are lacking.

Daily administration of doses of platinum of 0.1-100 mg/kg diet to rats did not induce effects in the fetuses.

Water-soluble platinum compounds

Experimental animal data indicate that soluble platinum compounds are irritating to the skin and corrosive to the eyes. Studies in mice confirmed the sensitising properties of chloroplatinum complexes and the lack of a sensitising potential of tetraammineplatinum dichloride.

No data were available from experimental animal inhalation studies. Oral LD_{50} values ranged from 10 to 100 mg platinum/kg bw. When soluble salts were administered to rats in the drinking water for four weeks, mainly effects on body weight (decreases) and kidneys (increased weights; impaired functioning) were seen at doses of ca. 50 mg platinum/kg bw. Generally, there were no effects at 10 mg/kg bw/day, but in some studies, there were decreases in haematological values (erythrocyte; haematocrit).

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 them were positive. Some of them were tested for other end points in other systems (*E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes: micronucleus test and comet assay), inducing both positive and negative results. *In vivo*, only dipotassium tetrachloroplatinate and tetraammineplatinum dichloride were tested, showing negative results in an erythrocyte micronucleus test in mice (single oral doses) and in a bone marrow chromosome aberration test in hamsters (repeated oral doses).

Data from carcinogenicity or relevant reproduction toxicity studies are lacking.

Evaluation and advice

Platinum and water-insoluble platinum compounds

Based on the available data, the committee cannot assess the potential genotoxic, carcinogenic, and reproductive effects following exposure to platinum and its insoluble compounds.

DECOS considers the toxicological database for platinum and water-insoluble platinum compounds too poor to recommend a health-based occupational exposure limit.

Water-soluble platinum compounds

Based on the available data, the committee cannot assess the potential genotoxic, carcinogenic, and reproductive effects following exposure to soluble platinum compounds.

The human and experimental animal data available indicate that chloroplatinates provoke sensitising and allergic effects of the respiratory tract and the skin while uncharged complexes and complexes with ligands other than halogens did not.

The committee is of the opinion that the Merget study indicates that there is a threshold for the sensitising effects of chloroplatinates: it does not expect that exposure to levels below 10 ng/m^3 causes sensitisation. The committee takes this value as a starting point for deriving a health-based occupational exposure limit. Applying a factor of 2 to account for the relatively small group involved (n=115), the committee recommends 5 ng/m^3 as a health-based occupational exposure limit, as an 8-hour time-weighted average. This limit value only holds for chloroplatinates.

Health-based recommended exposure limit

The Dutch Expert Committee on Occupational Standards of the Health Council recommends a health-based occupational exposure limit for chloroplatinates of 5 ng/m^3 (as platinum), as an 8-hour time-weighted average concentration.

The committee concludes that the toxicological database does not allow the recommendation of a health-based occupational exposure limit for soluble platinum compounds. However, the committee believes the data of Linnett and Hughes to indicate that an occupational exposure level of 0.5 µg/m^3 for tetraammineplatinum dichloride is not associated with toxicity, and might be used as an upper limit for workers.

Part I

Health Council of the Netherlands: Platinum and platinum compounds

Chapter 1

Scope

1.1 Background

At request of the Minister of Social Affairs and Employment (annex A), the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of existing substances that are used in the workplace. The purpose of the evaluations is to recommend a health-based occupational exposure limit for concentrations in the air, provided the database allows derivation of such a value. In the Netherlands, these recommendations serve as a basis in setting public occupational exposure limits by the minister.

1.2 Committee and procedure

This document is a co-production of DECOS and the Nordic Expert Group (NEG). It is a result of an agreement between both groups to prepare jointly criteria documents, which can be used by the regulatory authorities in the Netherlands and in Denmark, Iceland, and the Scandinavian countries. The members of DECOS and NEG are listed in annex B.

The joint draft document has been prepared by Birgitta Lindell, Ph.D. from the Swedish Institute for Working Life, Solna, Sweden, and was reviewed by NEG and subsequently by DECOS, before the final document was published by the Swedish National Institute for Working Life (Arbete och Hälsa 1997:14) in

1997. The final document is included in Part 2 of this report. Part 1 consists of a summary of the data presented in Part 2, presentation of data becoming available since 1997, and a discussion of the consequences of occupational exposure to platinum and platinum compounds. DECOS, hereafter called the committee, used these data in assessing a health-based occupational exposure limit.

In 2007, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of Part I of this report.

1.3 Data

In the sections below, a summary of the findings from the joint NEG/DECOS report on platinum (see Part II)* is presented firstly under 'NEG data' (in 'citaat' style), while any additional information from the literature searches is subsequently included in the paragraph 'additional information'.

Additional data were obtained from searches performed in February 2004 (for analytical aspects in April 2004) in the on-line databases Toxline, Medline, and Chemical Abstracts, starting from 1996. As key words, the names of the relevant platinum compounds and CAS numbers as listed in Table 1 (paragraph 2.1) were used, in combination with appropriate search profiles. For the classification and labelling of platinum compounds in the European Union the websites of the European Chemicals Bureau (ecb.jrc.it) and the N-class database of the Swedish Chemical Inspectorate (www.kemi.se/nclass/default.asp) were consulted. The analytical aspects of platinum and its salts were covered by searching the websites of CEN (www.cenorm.be), DFG (www.dfg.de), DIN (www.din.de), HSE (www.hse.gov.uk), ISO (www.iso.org/iso/en/isoonline.openerpage), NEN (www.nen.nl), NIOSH (www.cdc.gov/niosh/database.html), and OSHA (www.osha.gov).

The final search was performed in Medline in September 2007.

Note: the present report does not cover platinum-based drugs (particularly cytostatics/chemotherapeutics like cisplatin and its derivatives and carboplatin and its derivatives). Generally, these compounds are considered as carcinogenic to humans and classified as genotoxic carcinogens. In the Netherlands, for these compounds, the use of a threshold model for occupational standard setting is not deemed justified. Instead, an exposure-response relationship is recommended,

* References from Part II are referred to as 'NEGxx'.

i.e., the so-called health-based calculated occupational cancer risk values. For cisplatin, the Health Council published such values in 2005.

Chapter 2

Identity, properties and monitoring

2.1 Chemical identity

The basic data on platinum and relevant platinum salts are listed in Table 1.

2.2 Physical and chemical properties

Platinum (Pt) is a noble metal with atomic number 78. It belongs to group VIII of the periodic system, more precisely, the subgroup to which also nickel and palladium belong. The main oxidation states of platinum are +2 and +4; the first one is the most common.[NEG108] Platinum binds to a large number of inorganic and organic ligands, some of which (like cisplatin and carboplatin) have medical use as chemotherapeutic agents (and are not covered in the present report).[NEG60,NEG120] The physical and chemical properties of platinum and its salts covered in this report are listed in Table 2 (data from [NEG82]).

Table 1 Chemical identification of platinum and relevant platinum salts.

chemical name synomyms	formula	molecular weight	CAS number	EINECS number	EEC number	RTECS number
platinum platin, platinum metal, platinum black, platinum sponge, liquid bright platinum	Pt	195.09	7440-06-4	231-116-1	not listed	TP2160000
platinum oxide platinum monoxide, platinum(II) oxide, platinous oxide	PtO	211.08	12035-82-4	234-831-7	not listed	not listed
platinum dioxide platinum(IV) oxide, platinic oxide	PtO_2	227.08	1314-15-4	215-233-0	not listed	not listed
platinum monosulfide platinum(II) sulphide	PtS	227.15	12038-20-9	234-875-7	not listed	not listed
platinum disulfide platinum(IV) sulphide	PtS_2	259.21	12038-21-0	234-876-2	not listed	not listed
platinum dichloride platinum(II) chloride, platinous (di)chloride	$PtCl_2$	265.99	10025-65-7	233-034-1	not listed	TP2275000
platinum tetrachloride platinum(IV) chloride, 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 (chloro)platinic acid,(di)hydrogen hexachloroplatinate	H_2PtCl_6	409.81	16941-12-1	241-010-7	078-009-00-4	TP1500000
diammonium tetrachloroplatinate 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 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 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 potassium hexachloroplatinate(IV), platinic potassium chloride	K_2PtCl_6	485.99	16921-30-5	240-979-3	078-007-00-3	TP1650000
disodium hexachloroplatinate 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 platinumtetraammine dichloride, tetraamminedichloroplatinum(II) tetraammineplatinum(II) chloride	$[Pt(NH_3)_4]Cl_2$	334.11	13933-32-9	not listed	not listed	not listed

Table 2 Physical and chemical properties of platinum and its relevant salts.

chemical name	formula	molecular weight	melting point (°C)	density (kg/m³)	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	225-250 [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]	3.5	very soluble [e]
tetraammineplatinum dichloride	$[Pt(NH_3)_4]Cl_2$	333.98	250 [f]	2.7	soluble

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

2.3 EU classification and labelling

The platinum salts covered in this report which have been classified and labelled in the European Union are listed in Table 3. Platinum itself and some of its salts have not been classified/labelled (see Table 1).

2.4 Analytical methods

2.4.1 NEG data

The UK Health and Safety Executive (HSE) (method MDHS 46)[NEG22,NEG56], the US National Institute for Occupational Safety and Health (NIOSH) (method S191)[NEG110,NEG111] , and the US Occupational Safety and Health Administration (OSHA) (method ID121)[NEG116] have developed methods for the analysis of platinum metal and its soluble and insoluble salts in workplace air.

Although several techniques were described for the analysis of platinum in biological samples, there were no external quality assessment schemes for these analyses available, so these are not validated.

Table 3 Classification and labelling of relevant platinum salts.

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 – 22 – 26 – 36/37/39 – 45
diammonium tetrachloroplatinate $(NH_4)_2PtCl_4$	237-499-1	T; R25 Xi; R38-41 R42/43	2 – 22 – 26 – 36/37/39 – 45
diammonium hexachloroplatinate $(NH_4)_2PtCl_6$	240-973-0	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 45
dipotassium tetrachloroplatinate K_2PtCl_4	240-973-0	T; R25 Xi; R38-41 R42/43	2 – 22 – 26 – 36/37/39 – 45
dipotassium hexachloroplatinate K_2PtCl_6	240-979-3	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 45
disodium hexachloroplatinate Na_2PtCl_6	240-983-5	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 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).

2.4.2 *Additional data*

Air samples

HSE method MDSH 46 has been updated 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. 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-plat nates and other soluble platinum compounds. 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 to 8 hours for analysis by electrothermal atomic absorption spectrometry (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 times and 10 times the standard deviation of a blank determination, have been determined to be 3.6 and 12 ng/L for electrothermal AAS, and 0.003 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 and 4 µg/m^3 for electrothermal AAS, and 1 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).[1]

NIOSH has published another method for the determination of elements, including platinum, in air. This method – method 7303 (date: March 2003) – uses of the 'hot block' for digestion of the sampler. Sample solutions are analysed by inductively coupled plasma-atomic emission spectroscopy (IPC-AES).[2]

OSHA has described a specific method for the determination of platinum in workplace atmospheres (method ID-130-SG; date: March 1985). Air (containing particles) is collected on 0.8 µm cellulose membrane filters, with a sampling rate of 2 L/min; the recommended air volume is in the range between 250 L and 960 L. 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 graphite furnace atomic absorption spectrometry (GFAAS). The detection limit is reported to be 0.01 µg/mL.[3]

Biological samples

NIOSH has published methods for multi-element determinations (around 20 elements, among which platinum) in the matrices blood or tissue (method 8005; date: August 1994)[4] and urine (method 8310; date: August 1994).[5]

Blood and tissue samples are pre-treated by adding a digestion acid mixture and subsequent heating. Sample solutions are analysed using ICP-AES. For calibration, either external or internal standards can be used. The estimated limit of detection is reported to be 1 µg Pt/100 g blood and 0.2 µg Pt/g tissue. Furthermore, a recovery experiment with blood was carried out, and the quantity recovered is reported to be 92% of the spiked amount of platinum.[4]

Urine samples are pre-treated by adding polydithiocarbamate resin and subsequent shaking. After filtering samples, both filters and resins are ashed and acidified. Sample solutions are analysed using ICP-AES. The estimated limit of detection is reported to be 0.1 µg per sample urine; also a recovery experiment was carried out, but it was worse than the NIOSH criterion of ± 25% accuracy.[5]

The exposure to cytotoxic drugs in clinical practice of cancer treatment was studied among others for platinum as cisplatin and carboplatin. A method developed for the determination of platinum in urine using ICP-MS had a detection limit of 1.5 µg/L (8 pmol/L).[6]

Chapter 3

Sources and use

Platinum is a silver-grey noble metal of high commercial value due to its resistance to most corrosive agents and its excellent properties as an oxidation and reduction catalyst. In nature, it is a widely distributed but rare metal composing about 0.5×10^{-6} % of the earth's crust.

Platinum is obtained from mined ore and recycled metal. It is refined by treatment with aqua regia ($HCl:HNO_3$ 3:1) or HCl/Cl_2 yielding H_2PtCl_6, which is the general source of many other platinum compounds (see Part II).

In 2005, 2 million troy oz* (ca. 62 tonnes) of platinum were used in Europe, about 76% of which in the automotive industry (catalysts). Germany, UK, and France used about 4% and 2% in jewellery and in electronics, respectively, and Germany about 2% in dentistry. Worldwide, ca. 51% of the amount produced was used in the automotive industry, ca. 12% in jewellery, ca. 4% in electronics, and ca. 4% in chemical/petroleum refining; smaller amounts (ca. 1%) were used in dentistry and medicine (as anti-cancer drugs such as cisplatin and carboplatin). In 2005, the world supply of platinum amounted to ca. 7.2 million troy oz (ca. 225 tonnes), an increase of roughly 50% compared with the period 1995-2000. Most of this supply originated from mine production (ca. 78%), the remainder form Russian exports (ca. 10%) and secondary sources (10%) such as scrap (recovery from auto catalysts). South Africa is by far the major mine producer

* Platinum is usually quantified in ounces (oz; 1 oz = 28.3 g) or troy ounces (troy oz; 1 troy oz = 31.1 g). The literature is not always clear on which units are being used.

accounting for ca. 90%, followed by Canada (4%), Zimbabwe (3%), and the USA (2%). For 2006, an increase of about 10% is expected.[7] The production of platinum has generally followed its demand. Demands are expected to increase further due to the increasing demand for autocatalysts and the anticipated further development of fuel cells.[8]

Further details, including data on mining, refinery and use, are to be found in Part II of this report.

Chapter 4

Exposure

4.1 Ambient exposure

4.1.1 NEG data

Before the introduction of automobiles with catalytic converters for exhaust gases, the ambient air concentrations of platinum were dependent on the concentrations in nature, that is, in soil and fertilisers.[NEG3] In the 1970s, ambient air levels of generally less than 10 pg/m^3 were observed. Around 1990, levels of about 0.3-30 pg/m^3 were measured in Germany.[NEG3]

Platinum emissions from the generally used monolith-type catalysts in automobiles were calculated to be 2 ng/km (at 60 km/h) to 40 ng/km (at 140 km/h).[NEG78]

In a study from the 1970s, the total human daily intake of platinum in the UK was estimated to be less than 1 µg. This was based on analyses of a diet sample, but no data were given on the platinum content of the foods analysed.[NEG43]

4.1.2 Additional data

Ambient platinum air concentrations reported from 1995 onward for European cities including Frankfurt am Main, Göteborg, Madrid, Munich, and Rome are essentially similar to the concentrations mentioned above. Platinum in downtown airborne dust samples varied between 7 and 23 pg/m^3; for the ring roads of these

cities, the values varied between 4 and 18 pg/m³.[9,10,11] The tracheobronchial fraction (3.14-10.2 µm) represented approximately 21% and the alveolar fraction (<3.14 µm) approximately 14%.[10]

Artelt et al.[12] studied 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 and a 1.4 L engine). Depending on (combinations of) these conditions, mean platinum emissions ranged from 7 to 123 ng/m³ corresponding to emission factors between 9 and 124 ng/km. Platinum was almost exclusively bound to Al_2O_3 particles of which 43-74% had an aerodynamic diameter >10 µm; the alveolar fraction (<3 µm) ranged from 11-36%. Only a very small amount, i.e., ≤1%, of the total platinum emitted may consist of soluble platinum compounds.

In the so-called Total Diet Study, which is an important part of the UK Government's surveillance programme for chemicals in food, the mean total dietary exposure (i.e., not including the contribution from drinking water) for adults to platinum was estimated to be 0.2 µg/day (upper range: 0.3 µg/day). 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.[13]

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

4.2 Occupational exposure

4.2.1 NEG data

Occupational exposure to platinum may occur during mining, refining and processing, and manufacturing of platinum-containing products. The very scarce data of platinum air levels in mines indicate very low concentrations: <0.4 µg/m³.[NEG65] In refinery plants, levels of 0.02 µg up to 80 mg/m³ were reported, the highest levels (5-80 mg/m³) were noted in a poorly ventilated plant in China.[NEG149] In general, however, the available data indicate maximum levels of approximately 0.9-1.7 mg/m³.[NEG21,NEG37,NEG59,NEG95,NEG149] In recycling plants, the levels varied between 0.4 and 240 µg/m³ [NEG47]; for other platinum-applying industries, air levels of 0.1-20 µg/m³ have been published.[NEG42,NEG56,NEG139,NEG148] The UK Health and Safety Executive (HSE), which reviewed the available data in 1996, reported that

96% of all occupational exposure data (measured as 8-hour time-weighted average) were below 2 µg/m³. The majority of the data above 2 µg/m³ occurred during the production and dispensing of soluble platinum salts.[NEG56]

4.2.2 Additional data

At a catalyst-production plant in Germany, airborne platinum concentrations were measured at several areas in 1992 and 1993. For the area with the highest exposure, platinum levels of soluble platinum compounds in 1992 from roughly* 0.005 to 0.7 µg/m³ (16 measurements; sampling time: 12-17 hours). Median and upper and lower quartile values were 0.014 and 0.008 and 0.041 µg/m³, respectively. In 1993, levels ranged from roughly* 0.006 to 0.015 µg/m³ (12 measurements) with median and upper and lower quartile values of 0.037 and 0.012 and 0.064 µg/m³, respectively. Personal air sampling, performed in 1993, yielded higher concentrations. They ranged from roughly* 0.05 to 3.7 µg/m³ (22 measurements; 3 of them >2 µg/m³; sampling time: 8 hours). Median and upper and lower quartile values were 0.177 and 0.093 and 0.349 µg/m³, respectively. Concentrations of total platinum were ca. 10-fold higher.[15-17]

In the UK, soluble platinum concentrations were measured on two consecutive days at three different plants where three different processes were undertaken. In all cases, two different personal air samplers were used. On each day, four workers wore both devices; one designated for 'short-term' (generally 15 minute) and the other for 'long-term' (6-8 hour) samples while the designations were reversed the second day. In one plant, which was involved in the production of platinum catalysts, 'short-term' airborne soluble platinum levels (n=35) ranged from 0.02 to 10.82 µg/m³, with ca. 10% being >2 µg/m³; 50% were <0.5 µg/m³. The 8-hour levels (n=8) ranged from 0.03 to 0.6 µg/m³. In one of the other plants, where platinum and other precious metals were recovered, 'short-term' levels (n=35) ranged from 0.01 to 26 µg/m³, with 20% being >2 µg/m³; 50% were <0.3 µg/m³ (17% <0.01 µg/m³). The 8-hour levels (n=8) ranged from 0.06 to 13.6 µg/m³; two measurements were >2 Vg/m³). In the remaining plant, which produced metal-coated electrodes, 'short-term' levels (n=32) were between 0.03 and 0.99 µg/m³ (75% <0.03 µg/m³). The 'long-term' levels (n=7) ranged from 0.003 to 0.079 µg/m³.[18]

Concentrations of platinum in PM_{10} airborne samples, of total and soluble platinum in whole airborne samples, and of platinum in whole airborne samples collected by personal devices were measured in all departments of an industrial

* These ranges were estimated from a figure.

plant in Italy engaged in the production, recovery, and recycling of catalytic converters for the automotive traction and chemical industries. Based on personal air sampling, the highest levels were found in the coating department, followed by the recycling service, the metal dissolution department, and the process catalyst department. In the coating department and the recycling service, platinum seemed to be associated mainly with the fine fraction <10 µm while in the other areas, about 50% of the platinum was associated with the coarse fraction (i.e., >10 µm). The highest percentages of soluble platinum were found in the coating (mean ca. 30% of the total) and metal dissolution department (mean ca. 25% of the total). Mean platinum levels in the coating department were 1.21 µg/m^3 in PM_{10} airborne samples, 2.54 (total) and 0.67 (soluble) µg/m^3 in whole airborne samples, and of 2.70 µg/m^3 (range: 0.97-4.83 µg/m^3) in personal air samples.[19]

Chapter 5

Kinetics

5.1 Absorption

5.1.1 NEG data

Experiments in which rats inhaled radiolabelled Pt and soluble and insoluble platinum compounds (5-8 mg/m^3 for 48 minutes; particle size of soluble compounds: 1.0 µm) indicated little absorption. Most of the radioactivity was cleared from the lungs by mucociliary action, swallowed, and excreted via the faeces. The insoluble platinum compounds were longer retained in the lungs than the soluble ones.[NEG101]

Quantitative data on dermal absorption were lacking. In one experimental animal study, platinum was found in all internal organs, blood, and urine after dermal application of $(NH)_4PtCl_6$ [NEG133], but in a sensitisation study with rats and rabbits, no platinum could be detected in urine, serum, or spleen following repeated dermal application of $Pt(SO_4)_2$.[NEG157]

Gastrointestinal absorption appeared to be rather small, although soluble platinum salts were better absorbed than insoluble salts, PtO_2, or Pt (no quantitative data).[NEG19,NEG50,NEG85] However, a human study indicated a relatively large peroral uptake (at least 42%) of platinum from a hypothetical diet.[NEG168]

5.1.2 Additional data

Artelt et al.[20] investigated the bioavailability of finely dispersed platinum, similar to that emitted from motor vehicles equipped with catalytic converters. The num-

ber of platinum-containing particles in the exhaust from these vehicles is too low to collect sufficiently large amounts for animal studies. Therefore, a closely resembling model substance was synthesised, consisting of Al_2O_3 particles ≤5 µm (mean: 1.3 µm) onto which platinum particles ≥4 nm were deposited (Al_2O_3/Pt). In vitro, the solubility for Al_2O_3/Pt in pure water (0.4%) and in 0.9% NaCl (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 ascribed to the ultrafine structure of Al_2O_3/Pt, since an inverse correlation between the diameter of the platinum particles and the solubility was found. Further, part of the model substance was washed with saline. This washing procedure appeared to decrease the in vitro solubility in saline (0.1%). Obviously, the smallest platinum particles were 'removed' during this washing procedure. In the saline extracts, Pt(II) and Pt(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 (in saline) Al_2O_3/Pt to female Lewis rats by intratracheal instillation of amounts of 2 and 10 mg/animal once (1-day, 7-day study) or 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 90 days (see Table 4). In the inhalation study, flow rate, temperature, and aerosol concentration were continuously recorded. The mass median aerodynamic diameter (MMAD) of the aerosols was determined to be 1.3 µm.

The platinum contents of (only) the liver, spleen, kidney, adrenals, stomach, femur, and lung (and bronchoalveolar lavage (BAL) cells and supernatant), blood, urine, and faeces were analysed. The bioavailability was calculated by/expressed as Ax100/(A+B) (A: total Pt content in urine and all organs except the lung; B: retained Pt in the 'total' lung, i.e., lungs + BAL cell sediment + supernatant). Following inhalation of washed Al_2O_3/Pt complex, the bioavailability was ca. 23 and 31% for the high and low concentration, respectively. Following instillation, the bioavailability was ca. 4% at day 1, reaching values of 11-12% at post-instillation day 7 and of 9 to 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 4).

Table 4 Bioavailability of platinum in female Lewis rats after intratracheal instillation and inhalation [a] (from [20]).

	dose		study duration			
Al_2O_3/Pt	platinum powder	platinum	1 day	7 days	28 days	90 days
		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/m³ washed		160 µg				31.4%
12 mg/m³ washed		490 µg				22.7%

[a] Bioavailability after intratracheal instillation or inhalation was calculated by/expressed as: A x 100/(A + B); A = total platinum content and urine in all organs examined except the lungs; B = platinum retained in 'total' 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.

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 (see below). On the other hand, following intravenous injection of K_2PtCl_4, 41% of the total platinum were excreted within 10 days via the bile and faeces (see Section 5.3.2), suggesting that an unknown part of the platinum in the faeces following intratracheal instillation or inhalation originated from bioavailable platinum.

When rats were given a single oral (gavage) dose of 10 mg of Al_2O_3/Pt (see above), the bioavailability was calculated to be 0.1%, based on distribution of platinum in various body tissues, blood, urine, and faeces.[20]

5.2 Distribution

5.2.1 NEG data

In in vitro studies, protein binding of $(NH_4)_2PtCl_4$ and K_2PtCl_4 to serum albumin and transferrin was demonstrated.[NEG40,NEG156,NEG165] In human blood samples, most of the platinum was associated with protein; 65-80% was located in the erythrocytes.[NEG168]

During the first week after intravenous administration of radiolabelled platinum salts to rats, radioactivity was found in all tissues analysed: the largest amount in the kidney, the lowest amount in the brain. The decrease in tissue content of platinum roughly paralleled the decline of blood concentration.[NEG33,NEG99,NEG100]

Exposure to radiolabelled Pt or PtO_2 through inhalation (unknown particle size) led to immediate accumulation in the respiratory and gastrointestinal tracts. Next to these, kidney and bone were found to contain the highest concentration of radioactivity.[NEG101]

Oral administration of water-soluble platinum salts resulted in much higher platinum concentrations in blood and tissues than administration of comparable doses of Pt. Particle size was found to influence the tissue concentrations of platinum, particularly in the kidneys, but details of the particle sizes were not reported. In general, the absorbed platinum (orally given as Pt, $PtCl_2$, $PtCl_4$, or $Pt(SO_4)_2$) was distributed to virtually all organs and tissues; usually, the highest amounts were found in the kidneys, and the lowest amounts in adipose tissues and brain.[NEG5,NEG6,NEG19,NEG50,NEG85,NEG99,NEG100,NEG130]

Fetal uptake after administration of different platinum salts to pregnant rats and mice has been shown to be very low. In a study with intravenously administered radiolabelled $PtCl_4$ to pregnant rats, levels were measured 24 hours after dosing. The fetuses contained 0.01% of the dose per gram whole fetal tissue and 0.05% of the dose per gram fetal liver; placental levels were much higher (0.9% of the dose/g tissue).[NEG99]

Platinum levels in tissues of humans not occupationally exposed to platinum compounds varied greatly: from <1 to ca. 1200 ng/g wet tissue (liver, kidney, lung, heart, muscle) weight. Remarkably also in fat, significant platinum levels were observed.[NEG32,NEG65,NEG175,NEG181,NEG183]

5.2.2 Additional data

In agreement with earlier studies, Benes et al.[21] reported a great variation in the platinum content in 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 de range of 2-3920 (median: 2), 2.5-750 (median: 2.5), and 10-230 (median: 10) µg/

kg wet weight, respectively. No significant differences were seen between males and females.

Ten days following an intravenous injection of 1064 µg K_2PtCl_4 (total Pt: 500 µg/rat) to female Lewis rats, ca. 8% of the total platinum recovered was distributed among the organs (no details presented). When exposed by inhalation to 12 mg/m³ of washed Al_2O_3/Pt (see Section 5.1.2), 5 hours/day, 5 days/week, for three months, only ca. 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/m³, only ca. 0.003% was recovered with the highest amount in the kidney (0.016 µg).[20]

Zhong et al.[22,23] showed that subcutaneous administration of Na_2PtCl_6 to rabbits induced metallothionein synthesis in liver and kidney. Hepatic metallothionein contained little platinum (0.04 g atom/mol protein), while renal metallothionein contained higher platinum amounts (2.6 g atom/mol protein). The oxidation state of platinum in metallothionein was found to be +2. The results suggested that Pt(IV) complexes may be reduced *in vivo* to Pt(II) compounds and then bind to metallothionein. This process may play an important role in reducing the cytotoxicity of Pt(IV) complexes.

5.3 Elimination

5.3.1 NEG data

Limited data on excretion in humans indicate a slow elimination of Pt. In studies with a few platinum workers, no differences were found in urine and serum platinum levels at the start of a fortnight exposure-free period and at the end of this period.[NEG4,NEG168]

After intravenous administration of radiolabelled $PtCl_4$ to rats, the majority of the radioactivity was excreted into the urine and a lesser amount into the faeces. Thirty-five percent was excreted in the first three days, 86% after 28 days.[NEG33,NEG100]

After inhalation of several labelled platinum salts by rats, most of the radiolabel was excreted with the faeces during the first days; only small amounts were present in the urine (ratio faeces:urine 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 ten days more than 90% had been excreted.[NEG101]

$PtCl_4$ orally given to rats was mainly excreted via the faeces, suggesting that the majority had passed the gastrointestinal tract unabsorbed.[NEG99,NEG100]

5.3.2 *Additional data*

Schierl et al.[24,25] investigated the urinary excretion in humans. Thirty-four workers (32 men, 2 women) from a platinum refinery and catalyst production company were divided into four groups: (1) current high exposure (mainly K_2PtCl_4 and $Pt(NO_3)_2$), (2) former high exposure (stopped exposure 2-6 years ago because of hypersensitisation), (3) current low exposure (only occasionally exposed to lower levels), and (4) control group (no exposure). Sampling always included two spot urine samples, one at the end of a shift at the factory and a second one the next morning at home. For group 1, air platinum concentrations ranged from 0.2-3.4 µg/m³ (stationary) and from 0.8-7.5 µg/m³ (personal air sampling, PAS) with mean values of 1.1 and 2.5 µg/m³, respectively. For the control group, concentrations were <0.007 µg/m³. Urinary platinum excretion from workers after a shift (group 1) was found to be increased 1000 times up to 6270 ng/g creatinine. The urinary platinum excretion of the next morning was less increased (500 times; up to 2620 ng/g creatinine). Employees not exposed for several years (group 2) and free from symptoms still excreted 25 fold more platinum than the control group, indicating that there may be a long-lasting platinum pool in the body. Platinum excretion in occasionally exposed workers (group 3) was closer to the control group (increase: after a shift, 3-40 fold; at the next morning, 3-8 fold). Schierl et al.[24,25] investigated the excretion kinetics of platinum in more detail by exposing two human volunteers by inhalation to concentrations of $(NH_4)_2PtCl_6$ of 0.15 (person A) and 1.7 µg/m³ (person B), respectively (amount of platinum measured on filters in breathing zone: person A: 60 ng and person B: 800 ng platinum, measured on filters in the breathing zone) for four hours. Platinum excretion was measured in all urine sampled the next four days and in samples taken less frequently in the next four months. The excretion of platinum showed to be fast and dependent on exposure concentration. A steep increase (15 to 100 fold) in urinary platinum was found reaching its maximum nearly ten hours after inhalation: 23 ng/g creatinine in person A and 520 ng/g creatinine in person B (absolute levels of platinum excretion not given). Only in the case of high platinum exposure, the clearance was biphasic: for both persons a half-live of 50 h (95% confidence interval: 36-66 h) was calculated, while for person B a second half-life of 24 d (95% confidence interval: 18-33 d) was found (biphasic profile).

Following intravenous injection of 1064 µg K_2PtCl_4 (total platinum: 500 µg/rat) into female Lewis rats, ca. 50 and 41% of the total platinum were excreted within

ten days via the kidneys and urine and via the bile and faeces, respectively. Excretion via the faeces occurred somewhat faster than via the urine (roughly 60 and 70% within one and two days, respectively, vs. roughly 40 and 50%, respectively).[20]

5.4 Biomonitoring

5.4.1 NEG data

Background levels of platinum in blood and urine are suggested to be in the order of some nanogrammes per L (blood or plasma: <0.8-7 ng/L; urine: 0.5-15 ng/L), with a significant correlation between levels in blood, serum, and urine.[NEG34,NEG96,NEG139] Other reports indicate 100-200 times higher values (blood about 500-600 ng/L; urine: about 250 ng/L), but doubts have arisen as to the reliability of these analyses.[NEG67,NEG113, NEG114,NEG168]

A study of 40 occupationally exposed people showed mean platinum blood and serum levels of 39 and 39 ng/L, respectively, in the production section and of 125 and 75 ng/L, respectively, 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. Data concerning exposure time were not reported. 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.[NEG139]

In some other studies, lower blood and urine levels were observed.[NEG14,NEG65]

In Part II, analytical problems and difficulties in establishing reference values for platinum in blood and urine are outlined.

5.4.2 Additional data

Petrucci et al.[19] 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 industries and the most reliable biomarker for this exposure (see also Section 4.2.2). 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 mean percentage of soluble platinum in these samples was ca. 30%. The corresponding mean concentrations in urine, blood, and hair were 1860 ng/L, 380 ng/L, and 2260 ng/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 urine and 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 ng/L, respectively). Petrucci et al. 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. Farago et al.[26] 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 people, respectively. There was a significant correlation between the blood and urine levels. Schierl et al.[24,25] reported a mean urinary platinum concentration of 1994 ng/g creatinine (range: 170–6270 ng/g; 50 urine samples in total) in 15 'highly' occupationally exposed workers (mean exposure levels by personal air sampling: 2.5 µg/m^3; range: 0.8-7.5 µg/m^3). This was about 500 times the control value found in 12 unexposed persons (4 ng/g creatinine; range: 1-12 ng/g; 24 samples).

Further, Schierl et al.[24,25] found increased urinary platinum concentrations in four persons who stopped working in platinum industry two to six years before (forced by platinum allergy) (120 ng/g creatinine; range: 10–170 ng/g; 10 samples). These data suggest that platinum accumulates in the body following occupational exposure and is only released very slowly.

Background levels of platinum in urine can be derived from the German Environmental Survey 1998 (GerES III). This is considered to be a representative cross-sectional population-based study to determine the exposure of the general population to environmental contaminants, in which 4822 subjects, between 18 and 69 years of age from 120 localities, participated. A randomly selected subset of 1080 (out of 4741 available) morning urine samples were analysed for, amongst others, platinum. The number of teeth with noble metal dental alloy restorations appeared to increase urinary platinum excretion. The results did not show any relation between platinum in urine and parameters related to traffic. For samples from subjects (n=507) without dental restorations, mean, median, and geometric mean values of urinary platinum were 2.69 (range: <0.1-79.7), 1.50, and 1.32 (95% confidence interval: 1.19-1.46) ng/L, respectively (corrected for creatinine: 2.21, 1.1, and 0.99 ng/g creatinine, respectively). For subject with restorations (n=573), these values were 8.14 (<0.1-185), 3.4, and 3.38 ng/L.[27-29] Similar figures were seen in other German studies investigating smaller groups (ranging from10 to 92 subjects (see [29]).

In a US survey, the National Health and Nutrition Examination Survey (NHANES), in which male and female Mexican Americans and non-Hispanic

blacks and whites aged six years and older participated, urinary platinum concentrations were below the limit of detection (viz., 0.04 µg/L) in at least 95% of 5155 samples analysed over a four-year period (1999-2002).[30] In striking contrast, Paschal et al. reported very high platinum concentrations in urine samples from 496 subjects selected from some 30,000 participants in the NHANES conducted over the period 1988-1994. The study was performed to establish reference range concentrations for 13 metals in urine using ICP-MS (limit of detection: 0.4 µg/L). A mean urinary platinum concentration (without regard to age and sex) of 1260 ng/g creatinine with a 95% upper limit of 3590 ng/g was found (equivalent to 1520 ng/L with a 95% upper limit of 4220 ng/L).[31] The exact cause of these high values is unknown, but differences in analytical methods might (partly) have played a role.

5.5 Summary

Oral absorption of Pt and the insoluble platinum salts is very low (probably less than 1%), but via inhalation some absorption does occur. Soluble platinum salts are absorbed to a somewhat higher degree, both via the oral and the inhalation route of administration. Model experiments in which rats were exposed by inhalation to platinum (metal) particles ≥4nm deposited on Al_2O_3 particles ≤5 µm (closely resembling particles emitted from automotive catalytic converters) for up to 90 days suggested that up to ca. 30% of the platinum in this form deposited in the respiratory tract was bioavailable.

The generally small amounts of platinum that are absorbed are distributed to the soft tissues, especially the kidneys, and are sometimes also found in the bones. Excretion of bioavailable platinum appears to occur via a biphasic process, mainly in the urine; in humans, the two half-lives were approximately 50 hours and approximately 24 days, respectively. This indicates that platinum may accumulate in the body, which is supported by the finding of increased urinary platinum levels in individuals who stopped working in platinum industry several years before.

Data on biotransformation of platinum or its salts were not found.

Both in non-exposed and occupationally exposed persons, substantial variation has been observed in platinum levels in urine and blood, which might at least partly be due to differences and difficulties in analytical methodologies. Generally, background levels of platinum in blood and urine of non-occupationally exposed people will be in the order of magnitude of some nanogrammes per L or per gram creatinine (i.e., roughly <10). Platinum levels in blood and urine of

occupationally exposed people are much higher: in the order of magnitude of 50-150 ng/L in blood and 300-1200 ng/L (equivalent with approximately 250-1000 ng/g creatinine) in urine.

Chapter 6

Mechanism of action

6.1 Human studies

6.1.1 NEG data

The reactions of the respiratory tract and the skin that are seen in man after exposure to airborne soluble platinum salts are generally considered to be of immunological origin, but the precise sensitisation mechanism is unclear. Symptoms start after a sensitising period and a certain fraction of the exposed subjects become sensitised. Affected subjects become more and more sensitive to platinum and react to levels far below those normally encountered at work.[NEG94,NEG103,NEG120,NEG135,NEG177]

After skin prick testing in man with $(NH_4)_2PtCl_4$, Na_2PtCl_4, or K_2PtCl_4, or $(NH_4)_2PtCl_6$, Na_2PtCl_6, or K_2PtCl_6, an immunological type I reaction has been established. Other tests indicated also an IgE-mediated reaction.[NEG14,NEG21,NEG27,NEG29,NEG31,NEG58,NEG115,NEG127]

More details are presented in Chapter 7.

6.1.2 Additional data

Evidence that the sensitising potential of platinum compounds is restricted to the soluble halogenated compounds is accumulating. In addition to the data summarised in Part II, Linnett and Hughes[32] evaluated 20 years of medical surveillance on exposure to platinum compounds and demonstrated that a prerequisite for platinum compounds being allergenic is the need for a halide ligand coordi-

nated to platinum: chloroplatinates are clearly allergenic while $[Pt(NH_3)_4]Cl_2$, in which the halide is present as an ion, is not.

Studies with platinum salt-sensitised workers demonstrated strongly enhanced frequencies of specific T-cell receptors of peripheral blood mononuclear cells compared to non-exposed subjects. *In vitro* stimulation of peripheral blood mononuclear cells from workers as well as from non-exposed controls with Na_2PtCl_6 resulted in a time- and dose-dependent increase in specific T-cells.[33]

These and other studies are outlined in more detail in Chapter 7.

6.2 Animal studies

6.2.1 NEG data

Soluble platinum salts induced bronchoconstriction, anaphylactic shock, and elevated plasma histamine levels in experimental animals (monkey, dog, guinea pig, rat), either systemically or locally[NEG17, NEG120, NEG136]. Data obtained in monkeys indicate that Na_2PtCl_6 is a primary respiratory irritant producing bronchoconstriction.[NEG15]

Administration, via various routes including intratracheal, of conjugates of $(NH_4)_2PtCl_4$ with ovalbumine to rats induced IgE antibodies, while no specific IgE antibodies were induced in animals given the free platinum salt.[NEG103]

Immunogenicity of soluble platinum salts was demonstrated in mice by means of the popliteal lymph node (PLN) 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.[NEG143]

These and other studies are outlined in more detail in Chapter 7.

6.2.2 Additional data

In a number of studies investigating the immune response in mice using $(PtCl_4)^{2-}$ and $(PtCl_6)^{2-}$ salts, the following effects were found:

- 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-γ) in lymph node cells (essential for macrophage stimulation; suppression of the cell mediated immune response);
- 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 Chapter 7.

Chapter 7

Effects

7.1 Observations in humans

7.1.1 Irritation and sensitisation

NEG data

Occupational inhalation exposure to platinum salts (particularly the soluble ones) is a well-known cause of respiratory allergic manifestations and skin reactions. Symptoms include lachrymation, irritation of the upper respiratory tract, rhinitis and coughing, as well as angioedema and urticarial and eczematous skin lesions. True allergic contact dermatitis from exposure to platinum compounds, however, is rare.

Platinum compounds mainly responsible for sensitisation are H_2PtCl_6 and the chloroplatinate salts. Pt is not associated with hypersensitivity. Hypersensitivity usually develops within a few weeks to several years, and symptoms tend to get worse in time. Atopic as well as non-atopic workers may be affected[NEG23,NEG95,NEG115,NEG177], and smoking appears to predispose individuals to the development of platinum salt-induced sensitisation after occupational exposure.[NEG7,NEG23,NEG84,NEG170] It has also been proposed that concurrent exposure to irritants (like chlorine, ammonia, or ozone) potentiates the effects of platinum-salt exposure in a way similar to tobacco smoke.[NEG7,NEG109]

In a study with platinum-refinery workers with a known sensitivity to $(PtCl_4)^{2-}$ and $(PtCl_6)^{2-}$ salts, a number of platinum salts were used for skin prick tests. The results showed that a small group of charged complexes containing reactive halogen ligands were allergy-eliciting. The chloroplatinates were highly allergenic. Chloro ligands were most effective: changing from chloro to bromo ligands

reduced the response, while neutral complexes (such as *cis*--$[PtCl_2(NH_3)_2]$) 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.[NEG27] Other tests also indicated an IgE-mediated reaction.[NEG14,NEG29]

Several reports indicated a positive correlation between platinum-salt sensitisation and increased prevalence of rhinitis, asthma, and dermatitis symptoms.[NEG7,NEG14,NEG21,NEG23]

An overview of the prevalence of platinum-salt sensitisation in workers exposed to platinum salts is presented in Table 5.

Table 5 Prevalence of symptoms and positive skin tests in workers exposed by inhalation to soluble platinum salts (see Table 13, Part II).

total number of workers [a]	workers with symptoms (%)	workers with positive skin test (%)	Pt concentration in air (µg/m³)	country	reference
91	57	25	0.9 - 1700	UK	NEG59
20	60	42	nr [b]	USA	NEG131
11	73	nt [c]	nr	Germany	NEG89
16	88	nt	nr	Germany	NEG138
51	69	nt	nr	France	NEG120
91	54	26	nr	UK	NEG170
107	44	14	> 2	USA	NEG7,NEG14,NEG23
24	8	20	< 0.08	Germany	NEG94,NEG95
65	23	19	<0.1, < 2.0 [d]	Germany	NEG21

[a] Periods of employment were generally not reported.
[b] nr = not reported, platinum concentrations in air unknown.
[c] nt = not tested.
[d] Air monitoring resulted in platinum concentrations of <0.2 µg/m³ in 1984 and <0.1 µg/m³ in 1986; the German OEL of 2.0 µg/m³ was maintained throughout.

Additional data

Regarding irritation, additional data could not be located.

With respect to sensitisation, Koch and Baum[34] reported a case of 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. Patch tests with metal plates and metal salts (in the case of platinum: $(NH_4)_2PtCl_4$) showed a combined sensitisation to palladium and platinum. Histological examination showed an eczematous reaction on the test site of $(NH_4)_2PtCl_4$. Patch testing with small palladium and platinum metal plates showed a local strong positive reaction to palladium and a weak positive reaction to platinum. Three healthy volunteers tested with similar metal plates showed no adverse reactions. Four months after removing the dental palladium- and platinum-containing prostheses, the patient was free of lesions.

Dastychová and Semrádová[35] reported contact hypersensitivity to soluble platinum salts in a 42-year-old process worker in the manufacture of *cis*-$[PtCl_2(NH_3)_2]$ with a widespread papular eczema. The relevant substances tested from his working place, $K[Pt(NH_3)]Cl_3$ and K_2PtCl_4, 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.[36] investigated a group of 101 employees of a platinum refinery, comparing 44 of them with a positive skin prick test to $(NH_4)_2PtCl_6$ to 57 non-sensitised matching referents. They showed that the human leukocyte-associated antigen (HLA) phenotype was a significant determinant of sensitisation to $(NH_4)_2PtCl_6$.

In a Japanese factory, workers exposed to palladium, platinum, and rhodium (exposure levels unknown) showed type I hypersensitivity symptoms, such as urticaria, bronchial asthma, conjunctivitis, and rhinitis, and at the same time type IV 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 $PtCl_2$, disappearing a few hours later (immediate reaction). In the patch test with 0.5% $PtCl_2$, 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% $PtCl_2$ on filter paper attached on the nasal mucous membrane instantly produced severe rhinorrhoea, sneezing, wheezing, and asthma attack (dangerous situation). Curiously, all 12 patients tested showed normal values of serum IgE. Results confirmed the presence of both type I (immediate) and type IV (delayed) hypersensitivity in sensitised workers exposed to $PtCl_2$.[37]

Santucci et al.[38] compared the immunological responses on 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 H_2PtCl_6, K_2PtCl_4, and Na_2PtCl_6 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, two (1.3%) out of 153 subjects showed a positive patch test reaction to H_2PtCl_6 at day 2. One of these workers was also positive in the prick test to H_2PtCl_6. Another two subjects gave in the patch test to H_2PtCl_6 an urticaria reaction at 25 minutes. The wheals faded in three hours. Since in these patients platinum-specific antibodies were not identified, 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 22 (14.3%) workers (positive reaction: nine to all three platinum salts, six only to H_2PtCl_6, four to H_2PtCl_6 and K_2PtCl_4, three to H_2PtCl_6 and Na_2PtCl_6). Only four out of 22 were symptom free. The clinical manifestations were asthma, rhinitis, and/or urticaria. Results showed that the platinum salts tested did never cause positive reactions in subjects not occupationally exposed, whereas they elicited positive reactions in 22 out of 153 occupationally exposed patients. In addition, Santucci et al.[38] 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.

Calverly et al.[39] studied 78 recruits accepted for employment in a platinum-refining plant during two years in a prospective cohort 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. The results demonstrated that platinum-salt sensitivity was not predicted by pre-employment IgE status or testing for IgE antibodies specific to common inhalant allergens, but was subsequently associated with an increase in total IgE and conversion to positive responses in testing for allergen-specific IgE antibodies.

Raulf-Heimsoth et al.[33,40] determined the T-cell receptor (TCR) expression, additional cell surface molecules, proliferation of peripheral blood mononuclear cells (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 Na_2PtCl_6, and the IgE concentration was in the range of 17-657 kU/L (median: 110 kU/L). TCR expression was determined in isolated PBMCs by flow cytometry. The Na_2PtCl_6-mediated effects on the frequency of Vβ-expressing T-cells, the expression of other cell surface molecules, the proliferation response, and the cytokine production were studied *in vitro*. CD3-positive lymphocytes isolated from platinum-sensitised workers showed a significantly higher frequency of Vα2a+, Vβ11+, and Vβ21.3+ T-cells than controls. *In vitro*, the Na_2PtCl_6-

induced lymphocyte proliferation was enhanced in sensitised workers (SI*: 0.98-6.14, median: 1.68) compared to controls (SI: 0.2-2.9, median: 1.28). The incidence of enhanced PMBC proliferation was 53% (9/17) in sensitised workers, and 8.3% (1/12) in control subjects. *In vitro* stimulation with Na_2PtCl_6 of PBMCs from platinum-sensitised as well as control subjects showed modulation in the frequencies of certain T-cell subpopulations bearing specific V elements (increased percentage of Vβ5.3, Vβ6.7, Vβ8a/Vβ8, Vβ13.1, Vβ20, and Vβ21.3-positive CD3+ cells). Furthermore, a significant increase in CCR3-expressing T-cells was found (CXCR3 was not increased). The IL-4 production of T-cells (dose related) was enhanced, especially of sensitised workers (IFN-γ and IL-5 were not increased). In addition, IL-6, produced primarily by monocytes but also by T-cells, was significantly increased. Results showed that a particular T-cell receptor repertoire might be a useful biomarker or a possible risk factor for the development of platinum sensitisation.

Linnett and Hughes[32] presented a retrospective analysis of the 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 and who were followed up until 31 December 1995. They worked in one of three operations on the same site: the platinum-group metals refinery with exclusive exposure to chloroplatinates ('PGM refinery'; n=406), the autocatalyst production with exclusive exposure to $[Pt(NH_3)_4]Cl_2$ ('Autocat'; n=100), and the $[Pt(NH_3)_4]Cl_2$ production with mixed exposure ('TPC lab'; n=41). 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. Smoking habit was recorded before employment. The medical surveillance routine included enquiry about symptoms and skin prick tests every three months with three different chloroplatinates, and spirometry every six months. Criteria for diagnosis of allergy were set. The results of the analyses showed a significant difference in the incidence of allergy in these operations. In subgroups consisting of chemical process operators being exposed to platinum compounds for at least 50% of their work (n=270, 40, and 31, respectively), the cumulative change of being sensitised after five years of exposure was estimated to be 51% for chloroplatinate exposure, 0% for $[Pt(NH_3)_4]Cl_2$ exposure, and 33% for mixed exposure. The differences in sensitisation rates could neither be explained by age, sex, and atopy, nor by the increased frequency of smoking in the workers exposed to chlo-

* SI=stimulation index, defined as: 'the ratio of the mean radioactivity (counts per minute) obtained in the six similar cultures with allergen and that obtained in the allergen-free culture (medium control).'

roplatinates, despite the markedly higher risk of sensitisation in smokers. Analyses of the results of monitoring soluble platinum by personal sampling of the chemical process operators showed that ca. 90 and 52% of the values were below 0.5 µg/m³ and ca. 9 and 29% ≥2 µg/m³ in the 'PGM refinery' and 'TPC lab', respectively. In the 'Autocat', these figures (for $[Pt(NH_3)_4]Cl_2$) were ca. 61 and 9%, respectively (ca. 2% being >10 µg/m³).

Merget and co-workers[15-17] 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 performed in the period 1989-1995, and included a total of 275 employees of a catalyst-production plant in Germany, 115 of them working directly in the production lines ('high exposure'), 112 working regularly or irregularly within the catalyst department but not in the production lines ('low exposure'), and 48 who never entered the catalyst building ('no exposure'). Fifty-three per cent of the study population (for characteristics: see Annex D) were already present before the study; 47% were employed after the starting date of the study. The study population consisted further of subjects who had undergone at least 2 examinations and a negative response in the skin prick test against platinum at the initial survey. Skin prick testing was performed with a 10^{-2} mol/L H_2PtCl_6 solution. Merget et al. considered conversion from a negative response to a wheal diameter of 4 mm or larger as outcome variable in the analysis. Airborne platinum concentrations were measured in 1992 (n=16, 8, and 8 in the 'high', 'low', and the 'no exposure' area, respectively) and 1993 (n=12, 8, and 4, respectively) with a modified standard method for the detection of platinum, which defines soluble platinum by the amount of platinum that is dissolved in 0.07 mol/L HCl. Stationary sampling (of total dust) was carried out with a VC25 sampler with sampling periods varying between 12 and 17 hours. Because of the variation in sampling time and analytical procedures, the detection limits varied between 0.025 ng/m³ in 1992 and 0.13 ng/m³ in 1993. The dust was collected on glass fibre filters. Personal sampling (of inhalable dust) (n=22; sampling time: about 8 hours; 22 measurements) was performed in 1993 in highly exposed subjects (see also Section 4.2.2) using an Alpha 1 pump, a GSP head, glass fibre filters with a diameter of 37 mm*, and sampling times of about 8 hours. The limit of detection was about 20 ng/m³.

As summarised in Table 6, the results demonstrated that in a population of 160 workers, no new cases of sensitisation occurred during five-year exposure to airborne soluble platinum concentrations in the 'no' and 'low exposure' areas.

* R. Merget personal communication (e-mail to D.J.J. Heederik, 28 Feb 2007)

The maximum concentrations of soluble platinum measured in the 'low-exposure' area were 8.6 and 1.5 ng/m^3 in 1992 and 1993, respectively. 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 roughly 700 (1992) and 155 (1993) ng/m^3. Personal sampling in this area revealed a median value of 177 ng/m^3 with a highest value of 3700 ng/m^3; 3 measurements (out of 22) exceeded 2000 ng/m^3. Smoking cigarettes was positively associated with the occurrence of new symptoms.

Table 6 Platinum concentrations in workplace air and in sera of newly sensitised subjects (from Merget *et al.*[16]).

degree of exposure	no. of subjects	median concentrations of soluble platinum in ng/m^3 [a]			median concentrations of platinum in serum in ng/L	new sensitisations [b]
		area sampling 1992	area sampling 1993	PAS [c]		
no	48	0.05 (0.03-0.05) [d]	<0.13 (all)	not done	6.35 (<5-22.7)	0
low	112	6.6 (4.2-7.5)	0.4 (0.3-1.3)	not done	13.6 (<5-31.9)	0
high	115	14 (8-41)	37 (12-64)	177 (93-349)	38.2 (22.8-105) [e]	14 [f]

[a] Due to skewed data, only median values were presented (see footnote page 62).
[b] Based on a skin prick test conversion from a negative response to a 4 mm or larger wheal response with a 10^{-2} mol/L hexachloroplatinic acid solution.
[c] PAS = personal air sampling.
[d] Between brackets, lower and upper quartile, respectively.
[e] Significantly different from low exposure area ($p<0.02$) and from no exposure area ($p<0.006$).
[f] Includes one worker who was initially (mis)classified in the low-exposure category.

Obviously, exposures below the occupational threshold limit value (generally 2000 ng Pt/m^3) may still result in sensitisation. Even exposure to soluble platinum salts at levels between 10 and 100 µg Pt/m^3 may lead to sensitisation. Because other sources indicate that sensitisation to platinum salts rarely occurs after 5 years of exposure[41], the results of these prospective study suggest that at exposure to levels below 10 ng/m^3 sensitisation is not to be expected.

7.1.2 *Effects of single exposure*

NEG data

Acute poisoning was reported for a 7-month-old child who died five hours after accidental administration of 8 g of K_2PtCl_4.[NEG44]

A 31-year-old man who ingested 600 mg of K_2PtCl_4 suffered (among others) from vomiting, diarrhoea, leg cramps, renal failure, gastroenteritis, and leukocytosis. All symptoms disappeared within six days.[NEG180]

Additional data

No additional data were located.

7.1.3 Effects of repeated exposure

NEG data

There are no data concerning other effects than sensitisation and irritation (skin and mucous membranes) in humans repeatedly exposed to soluble platinum salts, and data on the potential health effects in humans following exposure to platinum metal or insoluble salts are completely lacking.

Additional data

No additional data were located.

7.1.4 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 found.

7.2 Animal experiments

7.2.1 Irritation and sensitisation

NEG data

In Table 7, data on skin and eye irritation of several platinum compounds are summarised.

Pulmonary hyperreactivity, expressed as significantly increased pulmonary flow resistance (R_L) and decreased forced expiratory volume ($FEV_{0.5}$/FVC), was found in male cynomolgus monkeys challenged with Na_2PtCl_6 aerosols (up to 62.5 mg/mL solutions; particle size: MMAD: 1.61 µm) two weeks after a period of repeated inhalation exposure to about 216 µg/m³ of the platinum salt (4 hours/day, biweekly for 12 weeks). No signs of bronchial hyperreactivity (compared to control group mean response) were found at an exposure level around 1940 µg/m³ without challenge, but marked effects on the pulmonary function were found in all exposed and control animals challenged with the platinum salt (control animals only after challenged with the highest concentration of Na_2PtCl_6). 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/m³ (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 in one week at an air level of 2 µg/m.[NEG17]

Table 7 Skin and eye irritation by platinum compounds [a] (data from [NEG63]).

compound	water solubility	skin irritation	eye irritation
PtO_2	insoluble	not irritating	-
$PtCl_2$	insoluble	not irritating	-
$PtCl_4$	slightly soluble	mildly irritating	-
$(NH_4)_2PtCl_6$	slightly soluble	mildly irritating	-
$(NH_4)_2PtCl_4$	soluble	slightly irritating [b]	corrosive
Na_2PtCl_6	very soluble	mildly irritating	irritating
$Na_2Pt(OH)_6$		severely irritating	-
K_2PtCl_4	soluble	not irritating	irritating
$K_2[Pt(CN)_4]$		mildly irritating	irritating [c]
$[Pt(NH_3)_4]Cl_2$		moderately irritating	strongly irritating
$Pt(NO_2)_2(NH_3)_2$	insoluble	not irritating	severely irritating

[a] Tests were carried out according to US Fed. Reg. 1973 guidelines or OECD guidelines.
[b] According to [NEG56], this compound produced pronounced skin irritation.
[c] According to [NEG56], this compound would currently not be classified as an eye irritant.

In further experiments with male cynomolgus monkeys, combined exposure to 200 µg/m³ $(NH_4)_2PtCl_6$ (MMAD: 1.07 µm) and 1 ppm ozone (6 hours/day, 5 days/week, 12 weeks) was shown to significantly reduce the concentration of Na_2PtCl_6 and methacholine needed to increase the mean R_L by 200%, which indicated that combined exposure increased both specific and non-specific bronchial hyperreactivity more than did exposure to either ozone or the platinum salt alone. Some animals with combined exposure exhibited extremely elevated R_L values and haemoptysis* after challenge with the most dilute solutions. Combined exposure also significantly increased the incidence of positive skin tests (intracutaneous test) to platinum when compared to exposure to platinum or ozone alone.[NEG16]

Conjugates of $(NH_4)_2PtCl_4$ and ovalbumine, administered via various routes including intratracheal, with adjuvant to female Hooded Lister rats, induced IgE antibodies (passive cutaneous anaphylaxis challenge, radioallergosorbent test), while no specific IgE antibodies were induced in animals given the free platinum salt (1 µg to 1 mg, similar routes)[NEG103]. In animals immunised with the conjugate, significant cross reactivity was seen between the conjugate, $(NH_4)_2PtCl_4$, and $(NH_4)_2PtCl_6$, while this was not seen with $Cs_2[Pt(NO_2)Cl_3]$, $K_2Pt(CN)_4$, $[Pt(NH_3)_4]Cl_2$, and *cis*-$[PtCl_2(NH_3)_2]$.[NEG104] In a later study, repeated injections of $(NH_4)_2PtCl_4$ (100 µg/kg bw, with adjuvant, three times per week for three weeks) to female Hooded Lister rats immunised

with ovalbumin as the antigen produced elevated levels of total IgE as well as specific IgE anti-ovalbumin antibodies.[NEG105]

* Expectoration of blood.

US EPA investigated the potential for skin sensitisation of $PtCl_4$ and $Pt(SO_4)_2$ in rats, mice, and guinea pigs. No allergic induction was shown when 50-350 µg/mL $Pt(SO_4)_2$ was repeatedly injected subcutaneously or intravenously, or when $Pt(SO_4)_2$ paste (0.1-0.25 g per application) was repeatedly applied to the skin. Also $PtCl_4$ 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.[NEG157]

Immunogenicity of soluble platinum salts was demonstrated in mice by means of the popliteal lymph node (PLN) assay. Differences were noted in the degree of response between the various mouse strains used (BALB/c, DBA/2, C57BL/6, B10.S, C3H/He, NMRI, NMRI+/nu, NMRInu/nu), and it was shown that mice deficient in T-lymphocytes completely failed to respond. A single subcutaneous injection of Na_2PtCl_6 or $(NH_4)_2PtCl_6$ (without adjuvant) induced a dose-dependent lymph node activation in C57BL/6 mice. Significant PLN reactions were induced at doses of about 1-8 mg/kg bw. Mice sensitised to $(PtCl_6)^{2-}$ mounted an enhanced response upon local stimulation with suboptimal doses (about one fifth of the primary dose) of the same compounds, but not when stimulated with unrelated compounds, which indicates a specific secondary response. Also equimolar amounts of Na_2PtCl_4 elicited a strong primary PLN response.[NEG143]

$(NH_4)_2PtCl_4$ 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%).[NEG9]

Additional data

Additional data on skin and eye irritation could not be located.

With respect to sensitisation, Mandervelt et al.[42] reported the sensitisation potential of Na_2PtCl_6 measured in the murine local lymph node assay (LLNA) with female BALB/c mice. Mice (n=3/group) received daily 25 µL of 0-2.5 % (w/v) Na_2PtCl_6 on the dorsum of both ears for three consecutive days by epicutaneous application. The draining auricular lymph nodes were excised 24 hours after the last exposure and the lymph node cells (LNC) were isolated. After 18 hours in culture, the *in vitro* cell proliferation was measured by counting [methyl-^{3}H]-thymidine (^{3}HTdR) incorporation and the stimulation index (SI; ratio of ^{3}HTdR incorporation from treated animals relative to that from control animals) was determined. Sensitisation with Na_2PtCl_6 yielded a maximal mean SI of 2.6±1.0 for the high-exposure group (2.5%). The total LNC number was more increased (about three fold) than the lymph node weight (about half as much).

In addition to Na_2PtCl_6, Schuppe et al.[43] investigated the capacity of other platinum salts (Na_2PtCl_4, K_2PtCl_4, and $[Pt(NH_3)_4]Cl_2$) to mount a primary immune response *in vivo* using the direct PLN assay. The results were compared with

their capacity to modulate mechanisms of receptor-mediated endocytosis in murine Langerhans cells *in vitro*. In the PLN assay, 45-900 nmol (15-300 ng/mL) of $[Pt(NH_3)_4]Cl_2$ or 90 nmol of the other platinum compounds were injected subcutaneously (one single injection) into one hind footpad of female BALB/c mice (n=5-7/group). On day 6 after treatment, cell numbers in the PLN of both the treated and untreated contralateral side were counted and the PLN index (ratio of cell count from the injected side relative to that from the untreated side) was determined. Both hexa- and tetrachloroplatinates induced vigorous primary PLN response with a maximal PLN index for Na_2PtCl_6. Flow-cytometric analysis revealed a dramatic increase (up to 20 fold for Na_2PtCl_6) in the total number of cells expressing proliferating cell nuclear antigen. The majority of these cells were of the T helper phenotype (CD4+) reflecting the T-cell dependence of the PLN response induced by platinum salts such as Na_2PtCl_6 or Na_2PtCl_4. In contrast, $[Pt(NH_3)_4]Cl_2$ failed to develop a prominent PLN reaction even at the highest concentration of 900 nmol (300 ng/mL). In the *in vitro* endocytosis assay, epidermal cells isolated from untreated BALB/c mice (sex and number not given) were pre-incubated with the mAb MK-D6 (anti-mouse I-A^d; binding to the I-A^d MHC class II alloantigen on Langerhans cells) and DTAF-conjugated secondary reagent for 15 minutes. The freshly prepared epidermal cells contained a mean of 2.5% Langerhans cells bearing MHC class II molecules. After washing, cells were stimulated for 30 minutes in the presence of 50-200 µM (23-91 µg/mL) Na_2PtCl_6, 250-2000 µM (96-770 µg/mL) Na_2PtCl_4, and 500-4000 µM (170-1340 µg/mL) $[Pt(NH_3)_4]Cl_2$. After a second wash and an incubation of two hours in the absence of platinum salts, internalisation of cross-linked I-A^d MHC class II molecules in Langerhans cells was determined by using a FACScan measuring the fluorescence intensity of internalised DTAF-coupled antibodies. Langerhans cells were identified by double labelling with mAb 2G9 (anti-mouse I-A^d, I-E^d; binding to newly expressed MHC molecules). For Na_2PtCl_6 and Na_2PtCl_4, a dose-dependent increase in endocytosis was found (Na_2PtCl_6 was more reactive than Na_2PtCl_4), whereas $[Pt(NH_3)_4]Cl_2$ did not modulate the internalisation. *Results 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. So, the in vitro endocytosis assay seemed to be useful for predicting the sensitising properties of platinum compounds in vivo.*

Schuppe et al.[44] further investigated the role of Na_2PtCl_6 in skin exposure (skin irritation, induction of contact hypersensitivity) by using the auricular lymph node (ALN) assay and a mouse ear swelling test (MEST). In the ALN assay, groups of five female BALB/c mice were exposed epicutaneously to 25

µL/ear/day of 0 and 5% (w/v) Na_2PtCl_6 on the dorsum of both ears for four consecutive days. One day after the last exposure, their bilateral draining ALNs were excised and pooled per animal. The total number of ALN cells was counted and the mean ALN index (ratio of cell counts from the treated group relative to that from the untreated group) was determined. The proportion of proliferating ALN cells ($PCNA^+$) was determined by staining for proliferating cell nuclear antigen (PCNA). Cells were further stained for CD4, CD8, and B220. In the MEST, on four or eight consecutive days groups of four to five female BALB/c mice (six- to eight-week old) were treated with 25 µL/day of 0 and 5% (w/v) Na_2PtCl_6 on the dorsum of the right ear. Some six days after treatment, animals were challenged on the left ear with Na_2PtCl_6 (0.5 or 2%). Left ear thickness was determined before and 0.5-72 hours after challenge and left ear specimens were taken for histological evaluation. Results were expressed as mean % increase in left ear thickness. In further experiments, the same groups of sensitised animals were repeatedly challenged. In the ALN assay, Na_2PtCl_6 revealed a four-fold increase in ALN cell yield. The proportion of proliferating cells ($PCNA^+$) among ALN cells of treated mice was increased over 20 fold. The majority of the proliferating $PCNA^+$ cells were $CD4^+$ T-cells. In the MEST, maximal swelling of the left ear was recorded at 48 hours in platinum-sensitised animals challenged with 2% Na_2PtCl_6. Upon repeated challenge, a significant response was detected even 20 weeks after initial treatment. After challenge, dermal oedema and infiltration of mononuclear and polymorphonuclear inflammatory cells characterised the contact hypersensitivity reaction. 5% Na_2PtCl_6 used for sensitisation caused an irritant reaction as demonstrated by persistent swelling of the right ear.

Dearman et al.[45] reported the cytokine production induced by topical application to mice of $(NH_4)_2PtCl_4$ and $(NH_4)_2PtCl_6$. Groups of female BALB/c mice (n=5/group; vehicle controls: n=10) were sensitised for cytokine production by application of 50 µL of 0-1% solutions of the platinum salts (in DMSO) bilaterally on each shaved flank. Five days later this treatment was repeated. After a further five days, 25 µL/day was applied to the dorsum of both ears for three consecutive days. Thirteen days after the initial exposure, draining auricular lymph nodes were excised and pooled per exposure group. The lymph node cells (LNC) were isolated and cultured for 12-120 hours in the presence or absence of concanavalin A to determine IL-4, IL-10, and IFN-γ production, respectively, in the supernatant. Trimellitic anhydride (TMA) (respiratory allergen: Th2-type cytokine production, i.e., IL-4 and IL-10) and 2,4-dinitrochlorobenzene (DNCB; contact allergen: Th1-type cytokine production, i.e., IFN-γ) were used as positive controls. The platinum salts (dose-related) and TMA stimulated vigorous IL-4 and IL-10 production, while DNCB and DMSO provoked substantial IFN-γ

expression. IFN-γ expression was lower by treatment with the platinum salts compared to the vehicle DMSO. The platinum salts exhibited an inverse dose-response relationship for IFN-γ expression, suggesting the elaboration of an inhibitory factor or factors for IFN-γ by Pt salt activated LNC. The induced type 2 cytokine secretion pattern was in agreement with the respiratory sensitising potential of the platinum salts *in vivo.*

In 2002, Chen et al.[46] reported that repeated administration of Pt(IV) salts might induce autoimmune disease. In female B10.S mice (prone to autoimmune effects; n=18-20/group) treated subcutaneously with Na_2PtCl_6 (1.7 mg/kg bw for eight weeks (three times/week), a platinum-induced production of anti-nuclear autoantibodies (ANA) was demonstrated. Dual-labelling revealed substantial co-localisation of these nucleoplasmic autoantigens with (1) nascent RNA, (2) the active, phosphorylated form of RNA polymerase II, and partial overlap with (3) acetylated histone 4 protein, and (4) 20S proteasomes in dendritic cells isolated from platinum-treated mice. Results suggested that platinum elicit antibodies against antigens associated with active sites of transcription which may be subject to proteasomal processing during platinum-induced autoimmunity.

Results of effects on the mouse immune system are summarised in Table 8.

In summary, studying the immune response in mice using the soluble platinum salts Na_2PtCl_4, Na_2PtCl_6, $(NH_4)_2PtCl_4$, and/or $(NH_4)_2PtCl_6$, the following effects were found (see also Table 8):

- 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-γ) in lymph node cells (essential for macrophage stimulation; suppression of the cell mediated immune response);
- stimulation of anti-nuclear autoantibodies.

Table 8 Effects on immunology measured in the mouse.

compound	species	assay	sensitisation	effects	reference
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	43-46
	mouse	endocytosis assay (Langerhans cells)		increased endocytosis	
	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	44
	mouse	assay on ANA [e]	24x sc	ANA[5] production	45
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 level	44,46
	mouse	endocytosis assay (Langerhans cells)		increased endocytosis	44
K_2PtCl_6	mouse	PLN assay	footpad (1x sc)	increased proliferation; Increased percentage of CD4+ T-cells	44
	mouse	endocytosis assay (Langerhans cells)		increased endocytosis	44
$[Pt(NH_3)_4]Cl_2$	mouse	PLN assay	footpad (1x sc)	no PLN reaction	44
	mouse	endocytosis assay (Langerhans cells)		no effect	44

[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.

In conclusion, the results confirm the sensitisation potential of soluble platinum salts like the tetra- and hexachloroplatinates, i.e., salts with a halogen ligand coordinated to platinum. $[Pt(NH_3)_4]Cl_2$, where there is no halogen ligand coordinated to platinum but present as an ion, failed to induce sensitisation.

7.2.2 *Effects of single exposure*

NEG data

Within a given class of platinum compounds, the expression of systemic toxicity is higher when administered by intravenous or intraperitoneal injections than by the oral route. Data regarding inha-

lation exposure were insufficient to allow for a ranking in the above route-dependent severity of toxicity.[NEG49,NEG50,NEG63,NEG108]

Clinical signs of acute toxicity of $(NH_4)_2PtCl_4$ include diarrhoea, clonic convulsions, laboured respiration, and cyanosis.[NEG63]

H_2PtCl_6 (40-50 mg/kg intraperitoneally) was highly nephrotoxic (severe tubular necrosis) in rats.[NEG171] $Pt(SO_4)_2$ administered to mice at the LD_{50} level (500 mg/kg intragastrically) affected their behaviour.[NEG85] Remarkably, pre-treatment of rats with a single lower dose of $PtCl_4$ 48 hours before a higher generally lethal dose of this salt was given markedly increased survival.[NEG51]

The oral LD_{50} values for rats vary greatly. They appear to be related to their water solubility, ranging from ca. 10 to 100 mg Pt/kg bw for soluble chloroplatinates[NEG63] to ca. >3000 mg Pt/kg bw for PtO_2.[NEG50]

Additional data

No additional data were located.

7.2.3 *Effects of repeated exposure*

NEG data

The main effects of platinum compounds after repeated administration are a decrease in weight gain and effects on the kidneys (increased weight; reduced function). In rats, these effects are generally seen at doses of approximately 50 mg platinum/kg bw/day during four weeks in the form of soluble salts in the drinking water ($PtCl_4$, $Pt(SO_4)_2$, or K_2PtCl_4). At doses of approximately 10 mg platinum/kg bw/day, toxic effects are absent except in some (but not all) studies that reported changes in haematological parameters (decreased erythrocyte and haematocrit counts). In contrast, at dietary doses of 700 mg platinum/kg bw/day to rats as PtO_2 during four weeks, no toxic effects were observed.[NEG5,NEG6,NEG49,NEG51,NEG100,NEG130]

Data on inhalation exposure were very scarce and unreliable.

Additional data

No additional data were located.

7.2.4 *Genotoxicity and cytotoxicity*

NEG data

The anti-neoplastic agent *cis*-[$PtCl_2(NH_3)_2$] 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 have also mutagenic activity. The results as reported in Part II are summarised in Table 9 in combination with additional data reported more recently.

K2$PtCl_4$ and $[Pt(NH_3)_4]Cl_2$ were negative in an erythrocyte micronucleus test in mice (single oral doses) and in a bone marrow chromosome aberration test in hamsters (repeated oral doses).[NEG56] No other *in vivo* data were available.

Additional data

Bünger et al.[47,48] reported the mutagenic and cytotoxic properties of the water-soluble platinum compounds $(NH_4)_2PtCl_6$, $(NH_4)_2PtCl_4$, and K_2PtCl_6 examined in two established mammalian cell lines (mouse fibroblast cell line L929, human embryonic lung cell line L132) by means of the neutral red test, and in bacteria (*S. typhimurium* strains TA97a, TA98, TA100, and TA102 with and without rat liver-derived metabolic activation). Cell lines were incubated for 24 hours with the platinum compounds at concentrations in the range of 0.06-10.00 mM. In L929 cells, a 50% reduction of cell viability (EC_{50}) was seen at 0.4, 0.3, and 0.2 mM for $(NH_4)_2PtCl_6$, $(NH_4)_2PtCl_4$, and K_2PtCl_6, respectively. In L132 cells, comparable EC_{50} values of 0.4, 0.8, and 0.6 mM, respectively were found (Table 10). Since the levels of toxicity of the different platinum complexes did not differ significantly from each other, platinum itself was assumed to be responsible for the toxic effects. In all *S. typhimurium* strains tested, a three- to 20-fold increase in mutation frequency was found (+/-S9) for the three platinum compounds (≥100 µg/plate), with a higher frequency for the platinum(II) than for the platinum(IV) compounds. Since all of the four test strains showed different mutations, the mutagenic effect of the platinum compounds were considered to result from several DNA-damaging mechanisms.

Gebel et al.[49] reported the genotoxic potential of the platinum salts $PtCl_2$, K_2PtCl_4, K_2PtCl_6, and $PtCl_4$ in the cytokinesis-block micronucleus test with human lymphocytes and the bacterial SOS chromotest. In the micronucleus test, lymphocytes obtained from blood taken from healthy, non-smoking, non-exposed donors (age: 25-35 years; number of donors unknown) were incubated

for 46 hours with 0-600 µM $PtCl_2$, 0-300 µM K_2PtCl_4, 0-40 µM K_2PtCl_6, and 0-60 µM $PtCl_4$. Before and during exposure, cells were stimulated with phytohaemagglutinin (PHA). In the SOS chromotest, *E. coli* strain PQ37 was incubated for 2.5 hours with 0-1213 µM for $PtCl_2$, 0-781 µM K_2PtCl_4, 0-367 µM K_2PtCl_6, and 0-481 µM $PtCl_4$. In the report of Gebel et al., the reported data in the text were not always in agreement with the data in the tables. Assuming the tables were most reliable, they were used for evaluation. K_2PtCl_4 and $PtCl_4$ were significantly genotoxic in both the micronucleus test (minimum genotoxic dose: 150 and 20 µM, respectively) and SOS chromotest (maximum induction factor: 3.63 and 4.54, respectively). $PtCl_4$ is a tetravalent platinum compound and was therefore presumed to be of lower genotoxicity than the divalent platinum coordination complex of K_2PtCl_4 (see Bünger et al.[47,48]). The potent genotoxicity of $PtCl_4$, however, may be caused by chemical reduction and/or by reasons of stereochemistry. K_2PtCl_6 and $PtCl_2$ did not reveal any genotoxic activity.

Migliore et al.[50] tested concentrations of 0-1000 µM of $PtCl_2$, 0-100 µM of $PtCl_4$, and 0-200 µM of $(NH_4)_2PtCl_4$ in a similar micronucleus test using lymphocytes obtained from a young, healthy, non-smoking, male donor (treatment time: 48 h). All three compounds produced statistically significant increases in the frequency of micronuclei at all (non-toxic) doses tested when compared with control values. $PtCl_4$ exerted the strongest action in terms of induction of micronuclei and cytotoxicity compared with the other divalent salts. Additional analysis with the fluorescence *in situ* hybridisation (FISH) technique revealed no significant difference in the frequency of centromere-positive and centromere-negative micronuclei for these compounds. This suggests that the induction of micronuclei is due both to clastogenic and aneuploidogenic mechanisms. Analysis by alkaline single cell gell electrophoresis (comet assay) of human leukocytes incubated with these salts for two hours showed oxidative DNA damage induced by $PtCl_4$ but not by the divalent platinum salts.

An *in vitro* study on cytotoxicity was reported by Mazzotti et al. in 2002[51]. They reported dose-effect curves and EC_{50} (50% inhibition of cell growth) values of $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ measured in the second stage of a programme for 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). $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ 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 replaced with non-treated culture medium. Seven days later, colonies containing ≥50 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 3.7±0.05 and 55±0.2 µM for $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$, respectively (Table 10). These results indicate that the cytotoxicity of platinum compounds is influenced by the chemical nature of the platinum compounds.

Table 9 Genotoxic activity of some platinum salts in *in vitro* test systems (NEG data and additional data).

compound	test system	metabolic activation	result	reference
$PtCl_2$	*E. coli* PQ37; SOS chromotest	-	-	50
	mouse lymphoma L5178Y cells; mutation assay	-	-	NEG137
	human lymphocytes; micronucleus test	-	-	50
	human lymphocytes; micronucleus test + FISH [a]	-	+	51
	human leukocytes; comet assay	-	-	51
$PtCl_4$	*S. typhimurium* TA98; mutation assay	-	+	NEG71
	S. typhimurium TA100, TA1535, TA1537, TA1538; mutation assay	-	-	NEG71
	E. coli B/r WP2 *try*, WP2 *hcr try*; mutation assay	-	-	NEG71
	E. coli PQ37 ; SOS chromotest	-	+	50
	B. subtilis H17 M45 ; rec-assay	-	+	NEG71
	D. melanogaster; sex-linked recessive lethal mutation assay		+	NEG179
	Chinese hamster lung V79 cells; mutation assay	-	+	NEG72
	Chinese hamster ovary S cells; mutation assay	-	+	NEG159
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	NEG159
	mouse lymphoma L5178Y cells ; mutation assay	-	+	NEG137
	human lymphocytes; micronucleus test	-	+	50
	human lymphocytes; micronucleus test + FISH [a]	-	+	51
	human leukocytes; comet assay	-	+	51
	Syrian hamster embryo cells; cell transformation assay	-	+	NEG26
$Pt(SO_4)_2$	Chinese hamster ovary S cells; mutation assay	-	+	NEG151,NEG158
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	NEG161
H_2PtCl_6	*S. typhimurium* TA98; mutation assay	+	+	NEG166
	S. typhimurium TA 100; mutation assay	+	-	NEG166
	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 ; mutation assay	-	-	NEG71,NEG166
	E. coli B/r WP2 *try*, WP2 *hcr try*; mutation assay	-	-	NEG71
	B. subtilis H17 M45 ; rec-assay	-	+	NEG71
K_2PtCl_4	*S. typhimurium* TA98, TA100	-/+	+/+	NEG79,NEG166
	E. coli PQ37; SOS chromotest	-	+	50
	S. cerevisiae ; assay for aneuploidy	-	+	NEG153
	D. melanogaster; sex-linked recessive lethal mutation assay		-	NEG56
	Chinese hamster ovary S cells; mutation assay	-	-	NEG158
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	NEG160
	Chinese hamster ovary K_1-BH_4 cells; mutation assay	-	(+) [b]	NEG57,NEG68
	human blood lymphocytes; micronucleus test	-	+	50

K_2PtCl_6	*S. typhimurium* TA97a, TA98, TA100, TA102 ; mutation assay	-/+	+/+	48 ,49
	E. coli PQ37 ; SOS chromotest	-	-	50
	Chinese hamster ovary S cells; mutation assay	-	+	NEG151,NEG158
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	NEG160
	human lymphocytes; micronucleus test	-	-	50
$(NH_4)_2PtCl_6$	*S. typhimurium* TA97a, TA98, TA100, TA102 ; mutation assay	-/+	+/+	48 ,49
	S. typhimurium TA	-		NEG71
	E. coli B/r WP2 *try*; mutation assay	-	-	NEG71
	E. coli WP2 *hcr try*; mutation assay	-	+	NEG71
	B. subtililis H17 M45 ; rec-assay	-	+	NEG71
$(NH_4)_2PtCl_4$	*S. typhimurium* TA97a, TA98, TA100, TA102; mutation assay	-/+	+/+	48 ,49
	human lymphocytes; micronucleus test + FISH [a]	-	+	51
	human leukocytes; comet assay	-	-	51
$[Pt(NH_3)_4]Cl_2$	*S. typhimurium* TA98, TA100 ; mutation assay	-/+	-/-	NEG166
	S. typhimurium TA100; mutation assay	not given	-	NEG79
	S. typhimurium TA98, TA100, TA1535, TA1538; mutation assay	not given	-	NEG56
	S. typhimurium TA1537; mutation assay	-/+	+/+	NEG56
	Chinese hamster ovary K_1-BH_4 cells; mutation assay	-	-	NEG57,NEG68
	D. melanogaster; sex-linked recessive lethal mutation assay		-	NEG56

[a] FISH = fluorescence *in situ* hybridisation; this technique enables to ascribe micronucleus induction to clastogenic or aneuploidogenic mechanisms.
[b] 'Marginally' positive.

Table 10 Cytotoxicity of some soluble platinum salts.

compound	indicator cell	EC_{50} [a] (mM)	reference
$(NH_4)_2PtCl_6$	L929, mouse fibroblasts cell line	0.4	39,40
	L132, human embryonic lung cell line	0.4	39,40
	Balb/3T3, mouse fibroblasts	0.0037	42
$(NH_4)_2PtCl_4$	L929, mouse fibroblast cell line	0.3	39,40
	L132, human embryonic lung cell line	0.8	39,40
	Balb/3T3, mouse fibroblasts	0.055	42
K_2PtCl_6	L929, mouse fibroblast cell line	0.2	39,40
	L132, human embryonic lung cell line	0.6	39,40

[a] EC_{50} = concentration at which 50% reduction of cell viability[39,40] or 50% inhibition of cell growth[42] was observed, respectively.

7.2.5 *Carcinogenicity*

NEG data

Except for *cis*-[$PtCl_2(NH_3)_2$] and some related compounds (which are known carcinogens), studies on the (potential) carcinogenicity of platinum metal and platinum compounds were not located.

Additional data

No additional data were located.

7.2.6 *Reproductive and developmental toxicity*

NEG data

The NEG data are summarised in Table 11.

Dietary administration of Pt or $PtCl_4$ (0.1-100 mg Pt/kg diet/day) to female Sprague-Dawley rats, for four weeks before pregnancy to gestational day 20, had no effects on the fetuses.[NEG18] When $PtCl_2$ or $PtCl_4$ (up to 100 mg Pt/kg diet/day) was given in the diet of lactating rats (21 days), no effects were seen in the offspring.[NEG77] Single oral (gavage) doses of $Pt(SO_4)_2$ (200 mg Pt/kg bw, ca. LD_1) to female Swiss ICR mice caused a reduction of pup weights when administered at gestational day 7 or 12, and a decreased activity when administered at lactational day 2. Similar, single subcutaneous treatment with Na_2PtCl_6 (20 mg Pt/kg bw, ca. LD_1) only resulted in decreased pup activity when administered on gestational day 12.[NEG30]

$PtCl_4$ (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.[NEG70]

Table 11 In vivo effects on reproduction and development (NEG data).

compound	species	exposure	effects	reference
Pt	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)	NEG18
$PtCl_2$	rat (female; Sprague-Dawley)	0.1-100 mg Pt/kg diet/day during lactation	no effect on offspring (weight; haematology)	NEG77
$PtCl_4$	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)	NEG18,NEG77
		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	NEG70
	mouse (male; Swiss)	0.5 mg Pt/kg bw/day, subcutaneous; for 30 days	largely decreased testis weights; spermatogenic arrest	NEG70
$Pt(SO_4)_2$	mouse (female; Swiss ICR)	200 mg Pt/kg bw, gavage; single dose gestational day 7 or 12	reduced offspring weight	NEG30
		post-natal day 2	decreased activity	
Na_2PtCl_6	mouse (female; Swiss ICR)	20 mg Pt/kg bw, subcutaneous; single dose gestational day 7 or 12	reduced offspring weight (only at day 12)	NEG30
		lactational day 2	no effect	

Additional data

The effect of platinum on spermatogenesis in mammals was studied in more detail in two recent *in vitro* experiments on Sertoli cells isolated from Sprague-Dawley rats (number not given)[52] and human sperm cells[53]. Sertoli cells were studied since, next to a direct toxic effect of platinum on sperm cells, alteration in Sertoli cell function may lead to impaired spermatogenesis and eventually to a reduced number of spermatozoa. Using cultured rat Sertoli cells, Monsees et al.[52] found that a 24-hour incubation period with 5-100 µM H_2PtCl_6 did not negatively affect cell viability (non-cytotoxic), but significantly stimulated mitochondrial dehydrogenase activity. Lactate production (essential for germ cell ATP production) was significantly enhanced up to 2.7 fold at 100 µM. Platinum further induced a biphasic response in the secretion of the Sertoli cell-specific hormone α-inhibin. α-Inhibin was significantly enhanced at 5-10 µM, but dropped again

in the higher concentration range reaching a significant decrease below the control value at >20 µM. α-Inhibin is important in early testicular development.

Eberl et al.[53] studied *in vitro* the effects of Na_2PtCl_6 and $[Pt(NH_3)_4]Cl_2$ on human sperm function and second messenger pathways. Washed human spermatozoa obtained from healthy donors (number not given) with normal sperm parameters according to the WHO, 1992 were treated with 0, 0.5, 5, 50, 100, and 1000 µM of both platinum salts during and after decapitation for three hours at 37°C. In addition, spermatozoa were incubated with platinum salts for three hours in calcium-free medium or in the presence of the protein kinase A+C inhibitor H7. The number of living acrosome-reacted spermatozoa was significantly and dose-dependently increased after incubation with both salts at all concentrations tested up to 25.0±2.9% for Na_2PtCl_6 and 21.0±5.8% for $[Pt(NH_3)_4]Cl_2$ at 1000 µM (control: 6.6±2.4%). Furthermore, sperm motility was markedly reduced at 1000 µM. An increased acrosome reaction was also seen when spermatozoa had first been decapitated. Calcium-free medium had no effect on the ability of both platinum salts to induce acrosome reaction, whereas the percentage of acrosome-reacted spermatozoa was reduced in the presence of H7. From the results, it was concluded that complex platinum salts influence sperm functions by inducing the acrosome reaction during or after decapitation. This stimulatory effect was independent of calcium and seemed to be dependent on protein kinase A or C.

The *in vitro* effects on reproduction are summarised in Table 12.

Table 12 In vitro effects on reproduction.

compound	species, cell type	exposure	effects	reference
H_2PtCl_6	rat [a], Sertoli cells	5-100 µM, 24 h	increased mitrochondrial dehydrogenase activity and lactate production; α-inhibin production: at 5-10 µM Pt: increased at >20 µM Pt: decreased	53
Na_2PtCl_6	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	54
$[Pt(NH_3)_4]Cl_2$	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	54

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

7.2.7 *Other effects*

NEG data

Soluble platinum salts administered to experimental animals have been shown to affect enzymes involved in haem biosynthesis (such as δ-aminolevulinic acid synthetase), the metabolism of xenobiotics (such as cytochtrome P450), malate dehydrogenase, and DNA synthesis (such as DNA polymerase). The tendency of platinum complexes to bind to nitrogen and sulphur in proteins might explain these effects.[NEG91] Also liver glutathione appeared to be affected. In general, a short period of decrease in activity is seen, followed by a period of increased activity. PtO_2 had only a marginal effect on these parameters.[NEG24,NEG36,NEG50,NEG51,NEG62,NEG73,NEG86,NEG117,NEG176]

Additional data

No additional data were located.

7.3 Summary and evaluation

The acute toxicity of platinum salts is low and depends on their solubility. Generally, the insoluble compounds are less toxic and irritating than the soluble ones. Oral LD_{50} data for rats range from ca. 10 to 100 mg Pt/kg bw for soluble chloroplatinates[NEG63] to ca. >3000 mg PT/kg bw for the insoluble PtO_2[NEG50]. In skin irritation tests, insoluble platinum compounds were not irritating while soluble compounds were slightly to severely irritating. In eye irritation tests, the soluble compounds were irritating to severely irritating or corrosive (no data on soluble compounds).[NEG56,NEG63]

The most significant health effect from exposure to soluble platinum compounds is sensitisation. Soluble platinum salts induce allergic reactions in which both the respiratory tract and the skin are involved. These reactions are caused by a humoral immune response, as was seen in exposed workers by increased levels of IgE, and in mice by an increased internalisation in Langerhans cells, lymph node cell proliferation and differentiation, and cytokine production induced by soluble platinum salts such as Na_2PtCl_4 and $(NH_4)_2PtCl_4$ and Na_2PtCl_6 and $(NH_4)_2PtCl_6$. Other platinum salts, i.e., complexes where there are no halogen ligands coordinated to platinum (such as e.g., $[Pt(NH_3)_4]Cl$, and neutral complexes (such as *cis*-$[PtCl_2(NH_3)_2]$) failed to induce such effects.

Obviously, H_2PtCl_6 and the $(PtCl_4)^{2-}$ and $(PtCl_6)^{2-}$ salts are the compounds mainly responsible for platinum-salt allergy: these compounds have apparently

the structural characteristics required to trigger sensitisation. All results together appear to indicate a dose-response relationship between the level of exposure and the extent of development of sensitisation. Sensitisation was shown to develop already at occupational exposure to airborne soluble platinum-salt levels of approximately 50-100 ng/m^3 (expressed as Pt), but not at levels <10 ng/m^3.[15-17] No sensitisation was seen in workers exposed to $[Pt(NH_3)_4]Cl$ at levels up to 2000 ng/m^3 (and occasionally >10,000 ng/m^3).[32]

Clinical symptoms of acute toxicity (including irritation/sensitisation) upon exposure to soluble platinum salts include lachrymation, irritation of the upper respiratory tract, rhinitis and coughing, as well as angioedema, urticarial and eczematous skin lesions; the latent period from the first contact to development of symptoms varies from a few weeks to several years.[NEG63,NEG171] The prevalence varies but covers roughly estimated some 50% of the workers. Skin prick testing before employment gives some indication of the sensitivity for developing allergic symptoms, but a negative test does not reliably predict the absence of this sensitivity.

No effects were observed when the insoluble PtO_2 was given for four weeks in the diet of rats at doses of 700 mg Pt/kg bw/day. When soluble salts were administered to rats in the drinking water for four weeks, mainly effects on body weight (decreases) and kidneys (increased weights; impaired functioning) were seen at doses of ca. 50 mg Pt/kg bw. Generally, there were no effects at 10 mg/kg bw/day, but in some studies, there were decreases in haematological values (erythrocyte; haematocrit). Data on carcinogenicity are lacking.

For the only insoluble platinum compound tested, viz., $PtCl_2$, *in vitro* tests for mutations (mouse lymphoma L5178Y cells)[NEG137] and DNA damage in bacteria (*E. coli*: SOS chromotest)[49] and mammalian cells (human lymphocytes: comet assay)[50] were negative. Both positive[50] and negative[49] results were reported in micronucleus tests in human lymphocytes. The induction of micronuclei was due both to clastogenic and aneuploidogenic mechanisms.[50] 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 them were positive. Some of them were tested for other end points in other systems (*E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes: micronucleus test and comet assay), inducing both positive and negative results.[47-50,NEG26,NEG48,NEG56,NEG57,NEG68,NEG71,NEG72,NEG79,NEG137,NEG151,NEG153,NEG158-NEG161,NEG166,NEG179]

In vivo, only K_2PtCl_4 and $[Pt(NH_3)_4]Cl_2$ were tested, showing negative in an erythrocyte micronucleus test in mice (single oral doses) and in a bone marrow chromosome aberration test in hamsters (repeated oral doses).[NEG56]

Data on reproductive and developmental toxicity are very limited. No effects were seen in rat fetuses (weight, resorptions, malformations) or pups (weight, haematology) following daily administration of doses of Pt or $PtCl_4$ of 0.1-100 mg Pt/kg diet, for 4 weeks before pregnancy to gestational day 20[NEG18] or in the offspring of lactating rats given similar daily doses of $PtCl_2$ or $PtCl_4$.[NEG77] Results from studies in which complex platinum salts were investigated *in vivo* (rat: single intratesticular injection; mouse: repeated subcutaneous injection)[NEG70] and *in vitro* experiments (human spermatozoa; rat Sertoli cells)[52,53] indicate that these salts 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).

Other effects reported with soluble platinum salts are effects on enzymes involved in haem biosynthesis, the metabolism of xenobiotics, DNA synthesis, and on liver glutathione.[NEG36,NEG50,NEG51,NEG86,NEG117]

Chapter 8

Existing guidelines, standards and evaluations

8.1 General population

The Regional Office for Europe of the World Health Organization (WHO) did not recommend a specific air quality guideline for platinum for the general population.[54]

8.2 Working population

Occupational exposure limits for platinum and platinum compounds in some European countries and the USA, listed in the most recent publications available to the committee (see page 84).

country - organisation	OEL (mg/m^3)		time-weighted average	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		55
Germany						
- DFG MAK-Kommission	-	-[c]			sens[d]	56
- AGS	-	-				57
Norway	-	0.002	8 h			58
Sweden	1[e,f]	0.002[f]	8 h		sens[g]	59
Denmark	1	0.002	8 h			60
Finland	1	0.002	8 h			61
Iceland	1	0.002	8 h			62
United Kingdom						
- HSE	5	0.002[h]	8 h	WEL		63
USA						
- ACGIH	1	0.002	8 h	TLV		64
- OSHA	-	0.002	8 h	PEL		65
- NIOSH	1	0.002	10 h	REL		65
European Union						
- SCOEL	1	-		IOELV		66

[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 occupational exposure limits.
[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] For total dust.
[g] For soluble platinum compounds.
[h] Certain chloroplatinates excepted.

8.3 Evaluations

- Health and Safety Executive (HSE)
  In its criteria document on platinum metal and its salts (published in 1996), the UK (HSE) concluded that exposure to the (soluble) chlorinated platinum salts leads to skin and respiratory hypersensitivity in humans, but stated that a conclusion as to the existence of a threshold for these effects is not possible. 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 $\mu g/m^3$ for soluble platinum salts.[NEG56]

- The American Conference of Governmental Industrial Hygienists (ACGIH)
  In its documentation of the TLV(s) of platinum and soluble compounds (from 2001), ACGIH concluded 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 sensitization had also occurred. According to ACGIH, the limited air sampling data indicated the need to maintain the concentration of airborne soluble platinum salts at a very low level to protect against the 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 sensitization. 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.[67]
- World Health Organization (WHO)
  In the Environmental Health Criteria document on platinum and platinum compounds of the International Programme on Chemical Safety (IPCS/ WHO) (published in 1991), it is concluded (1) that 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 sufficient 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 to assess the carcinogenic risk to humans of platinum or its salts are lacking.[NEG63]
- WHO: Regional Office for Europe
  In the second edition of the Air Quality Guidelines for Europe document (published in 2000), it is concluded that in occupational settings sensitisation reactions have been observed for soluble platinum down to the limit of detection of 0.05 µg/m^3, but that these effects have occurred only in individuals previously sensitised by higher exposure levels. It is further 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 thought to be required, in particular on the speciation of platinum in the environment.[68]

Chapter 9

Hazard assessment

9.1 Assessment of health hazard

9.1.1 Platinum metal and insoluble platinum compounds

The committee did not find data on the effects in humans following exposure to platinum metal or insoluble platinum compounds.

The committee did not find experimental animal data on sensitising or eye irritating properties of platinum metal or its insoluble compounds. PtO_2 and $PtCl_2$ were not irritating to the skin. The committee did not find acute inhalation data. Oral LD_{50} values in rats were greater than ca. 3000 mg Pt/kg bw.

The committee did not find data from repeated inhalation studies on platinum metal or its insoluble compounds. In a study in which PtO_2 was given to rats for four weeks at dietary doses of 700 mg Pt/kg bw/day no toxic effects were seen.

Data on carcinogenicity were lacking.

$PtCl_2$, the only insoluble compound for which genotoxicity data were available, did not cause mutations in mouse lymphoma cells or DNA damage in *E. coli* or human lymphocytes. Both negative and positive results were obtained in micronucleus tests in human lymphocytes. Further analysis of the positive test revealed that $PtCl_2$ may have both clastogenic and aneuploidogenic properties.

No effects were seen in rat fetuses (weight, resorptions, malformations) or following daily administration of doses of platinum of 0.1-100 mg/kg diet, for

four weeks before pregnancy to gestational day 20 or in offspring (weight, haematology) following administration of similar daily doses of $PtCl_2$ during lactation.

The committee is of the opinion that the data on the toxicity of platinum metal and insoluble platinum compounds are insufficient to allow recommendation of a health-based occupational exposure limit.

9.1.2 *Soluble platinum compounds*

Human data showed that the most significant risks from occupational exposure to water-soluble platinum salts are respiratory sensitisation and skin effects. Symptoms include lachrymation, irritation of the upper respiratory tract, rhinitis and coughing, as well as angioedema and urticarial and eczematous skin lesions. The prevalence of respiratory and/or cutaneous symptoms among workers involved in platinum refinery is frequently over 50% of the work force. Further, data indicate that platinum compounds with a halide ligand coordinated to platinum (i.e., chloroplatinates, such as H_2PtCl_6 and the $(PtCl_4)^{2-}$ and $(PtCl_6)^{2-}$ salts) provoke allergic reactions while other soluble complexes having ligands other than halogens (e.g., $[Pt(NH_3)_4]Cl_2$), do not. Linnett and Hughes[32], for instance, found that the cumulative chance of becoming sensitised after 5 years of exposure was 0% in a department with exposure to only $[Pt(NH_3)_4]Cl_2$ and 51% in a department with exposure to only $(NH_4)_2PtCl_6$. After skin prick testing with chloroplatinates, an immunological type I reaction has been established, also other tests indicated an IgE-mediated reaction.

In the five-year prospective cohort study by Merget and co-workers[15,16,17] sensitisation did not occur at exposure levels below 10 ng/m^3. Sensitisation after 5 years of exposure to platinum salts appears to be rare[41]. Therefore, the committee concludes that exposure to chloroplatinates at levels below 10 ng/m^3 is not expected to cause sensitisation.

The results of the Linnett/Hughes[32] study indicated that exposure to levels of $[Pt(NH_3)_4]Cl_2$ mostly below 0.5 µg/m^3 but occasionally higher than 2 or 10 µg/m^3 did not result in allergic reactions.

No other effects have been reported in workers occupationally exposed to soluble platinum compounds.

Experimental animal data indicated that soluble platinum compounds are slightly to severely irritating to the skin and irritating to severely irritating and corrosive to the eyes. Experiments in mice supported and confirmed findings on the sensi-

tising properties of the chloroplatinates and the lack of a sensitising potential of the other soluble salts in humans.

The committee did not find acute inhalation data. Oral LD_{50} data for chloroplatinates in rats range from ca. 10 to 100 mg Pt/kg bw.

Repeated inhalation studies were limited to studies investigating pulmonary hyperreactivity in monkeys. After repeated oral administration, mainly effects on body weights (decrease) and kidneys (increased weight; impaired functioning) at doses of ca. 50 mg Pt/kg bw/day for four weeks were seen; generally, no effects were seen at doses of 10 mg Pt/kg bw, but in some studies, there were decreases in haematological values (erythrocytes, haematocrit).

Data on carcinogenicity were lacking.

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 them were positive. Some of them were tested for other end points in other systems (*E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes: micronucleus test and comet assay), inducing both positive and negative results. *In vivo*, only K_2PtCl_4 and $[Pt(NH_3)_4]Cl_2$ were tested, showing negative results in an erythrocyte micronucleus test in mice (single oral doses) and in a bone marrow chromosome aberration test in hamsters (repeated oral doses).

Due to a lack of data from *in vivo* genotoxicity and carcinogenicity studies, the committee cannot assess the significance of the positive findings from *in vitro* studies.

No effects were seen in rat fetuses (weight, resorptions, malformations) or offspring (weight, haematology) following daily administration of doses of $PtCl_4$ of 0.1-100 mg/kg diet, for 4 weeks before pregnancy to gestational day 20 or during lactation, respectively. Soluble compounds have been shown to affect spermatogenesis. However, due to the design of these experiments (intratesticular or subcutaneous injection; *in vitro*), the committee cannot assess the significance of these findings for workers occupationally exposed to soluble platinum compounds.

9.2 Recommendation of a health-based exposure limit

9.2.1 Platinum metal and insoluble platinum salts

The committee is of the opinion that there are no data from which a health-based recommended occupational exposure limit can be derived for platinum metal and insoluble platinum salts.

9.2.2 *Soluble platinum salts*

Human and animal data indicate that soluble chloroplatinates are sensitising agents. Regarding inhalation of allergens at the workplace, the committee follows the approach as proposed recently by the Health Council.[69] The Health Council concluded that health-based occupational exposure limits can be recommended for allergens if adequate data on the existence of a threshold are present for the compound concerned. For the sensitising properties of $(NH_4)_2PtCl_6$, the committee is of the opinion that the five-year prospective cohort study by Merget and co-workers[15-17] provides reliable and valid data with respect to a threshold. Therefore, the committee uses the results of this study as a starting point for deriving a health-based occupational exposure limit. In the Merget study, sensitisation occurred in workers exposed to median levels of ca. 180 ng/m^3 (25 and 75% percentiles: ca. 100 and 350 ng/m^3; personal air sampling) but not at levels below 10 ng/m^3 (area sampling). Peak levels may have played a role, but its significance cannot be assessed. Taking 10 ng/m^3 as a starting point, the committee recommends 5 ng/m^3 as a health-based occupational exposure limit applying a factor of 2 to account for the relatively small group involved (n=115). This health-based recommended occupational exposure limit concerns soluble chloroplatinates.

The data from Linnett/Hughes[32] indicated that exposure to levels of $[Pt(NH_3)_4]Cl_2$ mostly below 0.5 µg/m^3 but occasionally higher than 2 or 10 µg/m^3 does not result in allergic reactions. However, the committee is of the opinion that these data cannot be used for deriving a health-based occupational exposure limit for soluble platinum compounds other than chloroplatinates, because a no-effect level could be (much) higher than 10 µg/m^3.

9.3 Groups at extra risk

From the data available, the committee identifies smokers as being more susceptible to the sensitising effects of soluble platinum salts compared with healthy non-smoking subjects. Furthermore, people with an already existing respiratory impairment would suffer particularly serious consequences if becoming sensitised.

9.4 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for chloroplatinates of 5 ng/m^3 (as Pt) as inhalable dust, as an 8-hour time-weighted average.

For platinum metal, insoluble platinum compounds, and soluble compounds other than chloroplatinates, no health-based occupational exposure limits can be recommended.

9.5 Additional consideration

The committee concludes that the toxicological database does not allow the recommendation of a health-based occupational exposure limit for soluble platinum compounds. However, the committee believes the data of Linnett and Hughes[32] (see page 90) to indicate that an occupational exposure level of 0.5 µg/m^3 for tetraammineplatinum dichloride is not associated with toxicity, and might be used as an upper limit for workers.

Chapter 10

Recommendations for research

Data on reproduction toxicology, genotoxicity, and carcinogenicity are very scarce or even lacking. To get a better insight into the toxicological profile of platinum and its water-soluble and insoluble salts, these data are indispensable.

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100 Platinum and platinum compounds

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as

part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the committee is given in Annex B.

Annex **B**

The committee

- G.J. Mulder, *chairman*
  emeritus professor of toxicology; Leiden University, Leiden
- R.B. Beems
  toxicologic pathologist; National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  toxicologist; Shell International BV, The Hague
- J.J.A.M. Brokamp, *advisor*
  Social and Economic Council, The Hague
- D.J.J. Heederik
  professor of risk assessment in occupational epidemiology; Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- L.A.L.M. Kiemeney
  professor of cancer epidemiology; University Medical Centre St Radboud, Nijmegen
- H. van Loveren
  professor of immunotoxocology; Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  occupational physician; Netherlands Center for Occupational Diseases, Amsterdam

- A.H. Piersma
  professor of reproductive toxicology; National Institute for Public Health and the Environment, Bilthoven
- H.P.J. te Riele
  professor of molecular biology; VU University Amsterdam, Amsterdam
- I.M.C.M. Rietjens
  professor of toxicology; Wageningen University and Research Centre, Wageningen
- H. Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T. Smid
  occupational hygienist - epidemiologist; KLM Health Services, Schiphol, and professor of working conditions, VU University Amsterdam, Amsterdam
- G.M.H. Swaen
  epidemiologist; Dow Benelux N.V., Terneuzen
- R.A. Woutersen
- toxicologic pathologist; TNO Quality of Life, Zeist
- P.B. Wulp
  occupational physician; Labour Inspectorate, Groningen
- J.T.J. Stouten, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of Part I of this report was prepared in 2004 by J. Draaijer and A.J. Baars from the National Institute of Public Health and the Environment, Centre for Substances and Integrated Risk Assessment, Bilthoven, the Netherlands, by contract with the Dutch Health Council.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether

the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2007 for public review. The following organisations and persons have commented on the draft report:

- E. González-Fernández, Ministerio de Trabajo y Asuntos Sociales, Madrid, Spain
- J. Reedijk, Leiden University, Leiden, the Netherlands
- R.D. Zumwalde, National Institute for Occupational Safety and Health, Cincinnati OH, USA

Annex **D**

Characteristics of the cohort studied by Merget *et al*.

	exposure group			
	high (n=115)	persistent low (n=51)	intermittent low (n=61)	no (n=48)
study group				
- catalyst department	104 (90.4%)	51 (100%)	4 (6.6%)	0
- craftsmen	11 (9.6%)	0	38 (62.3%)	1 (2.1%)
- controls	0	0	19 (31.1%)	47 (97.9%)
age (y)	32 (30-34)	32 (29-35)	39 (36-42)	38 (35-41)
males	115 (100%)	48 (94.1%)	60 (98.4%)	41 (85.4%)
smoking status				
- smokers	53 (46.1%)	16 (31.4%)	18 (29.5%)	16 (33.3%)
- non-smokers	24 (20.9%)	23 (45.1%)	24 (39.3%)	16 (33.3%)
- ex-smokers	38 (33%)	12 (23.5%)	19 (31.1%)	16 (33.3%)
- packyears	9 (7-11)	6 ((4-8)	9 (6-12)	11 7-15)
in plant before initial survey (mo)	31 (17-45)	72 (49-95)	144 (124-164)	123 (100-146)
occupational exposure time before initial survey (mo)	21 (15-27)	43 (30-56)	91 (75-107)	-
time between initial and final survey per subject (mo)	33 (29-37)	46 (40-52)	43 (38-48)	39 (33-45)
surveys per subject	4.6 (4,2-5.0)	5.3 (4.8-5.8)	5.3 (4.8-5.8)	4.5 (4.0-5.0)

Values represent arithmetic means or geometric means of skewed data with 95% confidence intervals or percentages in parentheses.
Of the study group of 275 subjects, 147 (53%) were employed before the study, 128 (47%) were newly employed during the study.

Part II

Arbete och Hälsa: Platinum

1997:14

DECOS and NEG Basis for an Occupational Standard

Platinum

Birgitta Lindell

Nordic Council of Ministers

ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE
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National Institute for Working Life

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Preface

An agreement has been signed by the Dutch Expert Committee for Occupational Standards (DECOS) of the Dutch Health Council and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic Countries.

This document on health effects of Platinum was written by Dr Birgitta Lindell from the Swedish Institute for Working Life in Solna, Sweden, and has been reviewed by the DECOS as well as by the NEG.

V.J. Feron
Chairman
DECOS

P. Lundberg
Chairman
NEG

Contents

Abbreviations

AAS	Atomic absorption spectrometry
8-AG	8-azaguanine
AV	Adsorptive voltammetry
CHO	Chinese hamster ovary
EPA	US Environmental Protection Agency
FAAS	Flame atomic absorption spectrometry
FEF_{25}	Forced expiratory flow at 25% of vital capacity
$FEV_{0.5}$	Forced expiratory volume in 0.5 second
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GFAAS	Graphite furnace atomic absorption spectrometry
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
HSE	UK Health and Safety Executive
I_{50}	Concentration required to produce a 50% inhibition
ICP-AES	Inductively coupled plasma atomic emission spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
IgE	Immunoglobulin E
IPCS	International programme on chemical safety
LC_{50}	Inhalation concentration that is estimated to be lethal to 50% of test animals
LD_1	Dose that is estimated to be lethal to 1% of test animals
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
LOAEL	Lowest observed adverse effect level
MMAD	Mass mean aerodynamic diameters
NIOSH	US National Institute for Occupational Safety and Health
NOAEL	No observed adverse effect level
OEL	Occupational exposure limit
OSHA	US Occupational Safety and Health Administration
OVA	Ovalbumin
PCA	Passive cutaneous anaphylaxis
PCE	Polychromatic erythrocyte
PLN	Popliteal lymph node
ppm	Parts per million (in air or in diet)
RAST	Radioallergosorbent test
R_L	Pulmonary flow resistance
SHE	Syrian hamster embryo
TWA	Time-weighted average

1. Introduction

The use of platinum has increased worldwide during the last 20 years. Large amounts of platinum are used e.g. in the chemical and petroleum industry, but the increased demand for platinum mainly is dependent on the introduction of the automobile catalytic converter systems. In this document relevant studies concerning platinum metal and various platinum compounds have been reviewed, but studies on the anticancer drug cisplatin and analogues usually have been excluded. The possibility to draw general conclusions on platinum toxicity, relevant for the work environment, from data on cisplatin is limited. The handling of cisplatin and its analogues e.g. by pharmacy and hospital personnel is a special case of possible occupational exposure. In most Nordic countries instructions for handling cytostatic drugs are available. Furthermore, a summary of current knowledge of chemical health risks (including cytostatics) for health care personnel in the Nordic countries has been published recently (163).

2. Chemical identification

Chemical formula, molecular weight and CAS numbers of some platinum compounds are listed in Table 1.

3. Physical and chemical properties

Platinum is a relatively soft and ductile, silvery metal with the atomic number 78 and belonging to group VIII of the periodic system (12). Platinum occurs mainly as the isotopes ^{194}Pt (32.8%), ^{195}Pt (33.7%) and ^{196}Pt (25.4%) (108). Platinum is relatively inert, with respect to chemical attack by oxygen or many acids, but the chemical reactivity is markedly influenced by the state of subdivision of the metal (108). Platinum does not visually exhibit an oxide film when heated, although a thin adherent film forms below 450°C. Above this temperature platinum slowly loses weight because of the formation of the volatile oxide (PtO_2) (2). Platinum metal can be affected by halogens, cyanides, sulfur, molten sulfur compounds, heavy metals, and hydroxides (63). It can form alloys and its tendency to form complexes is strong (60, 120). The principal oxidation states of platinum are +2, +4 and 0; of these, the first is the most common (108). The highest oxidation state of the element is +6 (platinum hexafluoride) (46, 90).

Platinum binds to a large number of ligands (ions or neutral molecules), some of which have more than one binding site, to form neutral or charged complexes or salts. The divalent compounds are predominantly four-coordinate and square planar, the tetravalent compounds six-coordinate and octahedral and the zerovalent compounds four-coordinate and tetrahedral (22, 46). Halogen- and nitrogen-donor

Table 1. Chemical identification of some platinum compounds

Chemical name (Synonyms)	Chemical formula	Molecular weight	CAS number
Platinum (platin, platinum metal, platinum black, platinum sponge, liquid bright platinum)	Pt	195.09	7440-06-4
Platinum(II) oxide (platinous oxide, platinum monooxide)	PtO	211.08	12035-82-4
Platinum(IV) oxide, (platinic oxide, platinum dioxide)	PtO_2	227.08	1314-15-4
Platinum(II) sulphide	PtS	227.15	12038-20-9
Platinum(IV) sulphide	PtS_2	259.21	12038-21-0
Platinum(II) chloride (platinous chloride, platinous dichloride, platinum dichloride)	$PtCl_2$	265.99	10025-65-7
Platinum(IV) chloride (platinum tetrachloride, tetrachloroplatinum)	$PtCl_4$	336.89	37773-49-2 (pentahydrate: 13454-96-1)
Hexachloroplatinic(IV) acid (chloroplatinic acid, platinic acid, dihydrogen hexachloroplatinate, hydrogen hexachloroplatinate)	H_2PtCl_6	409.81	16941-12-1 (hexahydrate: 18497-13-7)
Ammonium tetrachloroplatinate(II) (ammonium chloroplatinite, diammonium tetrachloroplatinate, platinous ammonium chloride)	$(NH_4)_2PtCl_4$	372.97	13820-41-2
Ammonium hexachloroplatinate(IV) (diammonium hexachloroplatinate, platinic ammonium chloride)	$(NH_4)_2PtCl_6$	443.87	16919-58-7
Potassium tetrachloroplatinate(II) (potassium chloroplatinite, dipotassium tetrachloroplatinate, platinous potassium chloride)	K_2PtCl_4	415.09	10025-99-7

Table 1. Cont.

Chemical name (Synonyms)	Chemical formula	Molecular weight	CAS number
Potassium hexachloro-platinate(IV) (dipotassium hexachloroplatinate, platinic potassium chloride)	K_2PtCl_6	485.99	16921-30-5
Sodium hexachloro-platinate(IV) (disodium hexachloroplatinate, sodium platinum chloride)	Na_2PtCl_6	453.77	16923-58-3

*derived from RTECS data lists 1996; Registry file STN 1996; Ref. 56, 82).

ligands are common, but in the divalent oxidation state platinum readily form complexes with ligands containing donor atoms from most groups of the periodic Table (46). Several of these chemicals exist as cis and trans isomers and the geometric arrangement is of great importance in biochemical processes (63, 73, 166, 178).

The compounds vary in colour from yellow (e.g. ammonium hexachloroplatinate (IV), platinum sulphate), to olive-green (e.g. platinum(II) chloride), to red/red-brown (e.g. ammonium tetrachloroplatinate(II), platinum(IV) chloride), and to black or almost black (platinum(II) sulphide, platinum(IV) sulphide, platinum(IV) oxide) (2, 12, 82, 90, 154, 172). The solubility in water also differs between platinum compounds (154). Platinum metal and platinum oxides are insoluble, while e.g. the complex salts ammonium hexachloroplatinate(IV) and potassium hexachloroplatinate(IV) are sparingly soluble in water. The tetrachloroplatinates ammonium tetrachloroplatinate(II) and potassium tetrachloroplatinate(II) are more easily soluble than the corresponding hexachloroplatinates. Some constants of platinum and various platinum compounds are given in Table 2.

4. Occurrence, production and use

4.1. Occurrence

Platinum is a widely distributed but rare metal composing about $5x10^{-7}$% of the earth´s crust (3). In its native state, platinum generally is alloyed e.g. 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 (59, 108, 120). The principal minerals containing platinum are sperrylite ($PtAs_2$), cooperite (Pt,Pd)S and braggite (Pt,Pd,Ni)S (90).

Table 2. Some chemical and physical data* for platinum and some platinum compounds

Chemical name	Melting point	Boiling point	Density (g/cm^3)	Solubility in water
Platinum	1768°C	3825°C	21.45 (20°C)	insoluble
Platinum(II) oxide	325°C decomp	-	14.1	insoluble
Platinum(IV) oxide	450°C	-	11.8	insoluble
Platinum(II) sulphide	-	-	10.25	insoluble
Platinum(IV) sulphide	225-250°C decomp	-	7.85	insoluble
Platinum(II) chloride	581°C decomp	-	6.0	insoluble
Platinum(IV) chloride	327°C decomp	-	4.30	slightly soluble
Platinum(IV) chloride (pentahydrate)	-	-	2.43	soluble
Platinum(IV) sulphate (tetrahydrate)	-	-	-	soluble
Hexachloroplatinic(IV) acid (hexahydrate)	60°C	-	2.43	very soluble
Ammonium tetra-chloroplatinate(II)	decomp	-	2.94	soluble
Ammonium hexa-chloroplatinate(IV)	380°C decomp	-	3.07	slightly soluble
Potassium tetrachloro-platinate(II)	500°C decomp	-	3.38	soluble
Potassium hexachloro-platinate(IV)	250°C decomp	-	3.50	slightly soluble
Sodium hexachloro-platinate (IV)	250°C decomp	-	3.5	very soluble (hexahydrate)

*derived from 12,56,82,154,172.

The occurrence of platinum in ambient air before the introduction of cars with catalytic converters was mainly dependent on the concentration in nature (e.g. in soil particles, fertilizers) (3). When platinum concentrations in road dusts were analysed in Sweden in 1984 and 1991 a significant increase in platinum concentration was found in all fractions in 1991 (174). Few measurements of platinum in ambient air have been reported. The levels of platinum in 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 (67). Mean concentration of platinum in 1973 near a highway outside the city of Ghent (Belgium) was reported in another study (146) to be less than 10 pg/m^3. In Germany, platinum air concentrations were measured close to city roads in 1989 and found to be up to 13 pg/m^3. In rural areas the concentrations were at most 1.8 pg/m^3 (Tölg & Alt, 1990 cited in 63). At that time few German cars were equipped with catalysts and thus these levels could reflect background levels. The platinum emission from the monolith-type catalysts used in Europe has been calculated to be 2 ng/km travelled at a speed of 60 km/h and about 40 ng/km at a speed of 140 km/h (78). Based on dispersion models used by US 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 in a roadway tunnel) (63, 78). In a more recent study (3) air levels of 0.3 to 30 pg Pt/m^3 were measured in Germany. 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 USA, only 10% of the platinum emitted was water-soluble (134, 135). At temperatures above 500°C (as in the exhaust converter) metallic platinum reacts with oxygen to form platinum(IV)oxide (8, 134). According to an evaluation made by IPCS, it is not possible to conclude if microorganisms in the environment are able to biomethylate platinum compounds. For further details on the occurrence of platinum in the environment see references 3 and 63.

When platinum levels in blood, hair and urine were measured in Australia no significant difference in the Pt concentration between residents in high or medium polluted or unpolluted areas was found (113, 168). The concentrations of total platinum in a range of foodstuffs from Sydney (prepared by normally used cooking methods) also was determined (168). The levels of platinum were between 8.11 μg/kg (liver) and 0.13 μg/kg (full-cream milk). Food-groups containing high levels of platinum were meat (0.7-5.7 μg/kg; mean 3.2) and grain products (0.6-5 μg/kg; mean 3.2). Eggs also contained high levels of platinum (about 3.5 μg/kg), whereas low levels of platinum were found in fruit and vegetables (0.2-2.1 μg/kg; mean 0.82) and dairy foods (mean 0.27 μg/kg). Calculations based on these values showed the large contribution of the diet to the Pt levels in humans. The total dietary intake of Pt for an adult Australian was calculated to be about 1.4 μg/day (female: 1.15 μg/day; male: 1.73 μg/day) (168). However, when the baseline levels of platinum e.g. in blood were determined by these authors the obtained values were very high compared to the values obtained by other researchers. Thus, the reliability of the platinum levels in food might be questioned too. In an older study from United Kingdom a total daily intake of less than 1 μg platinum was estimated, based on an analysis of a diet sample, but no data were given on the platinum content of the foods analysed (43).

4.2. Production

Platinum is obtained from mined ore and recycled metal (58). The ore is concentrated following flotation and smelting operations, and individual metals are separated

and refined by a complex chemical treatment. During the refining the concentrate is dissolved in aqua regia or hydrochloric acid/ chlorine. Hexachloroplatinic(IV) acid or sodium hexachloroplatinate(IV) (after treatment with sodium chloride) is formed and in both cases addition of ammonium chloride leads to formation of ammonium hexachloroplatinate(IV) (yellow salt) (58, 63, 120, 138). After calcination at 600-700°C a crude platinum metal sponge is formed, which undergoes further refining. Finally, after heating up to 1000°C a grey metal sponge of platinum >99.9% pure is produced (46, 58, 120). 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 (12, 60, 63). Platinum and its alloys are manufactured e.g. into sheet, wire, and foil for use in jewellery, dentistry, and in the electrical and chemical industries (59, 90). 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 (12, 108).

Intensive studies have been made to find useful anticancer drugs similar to cisplatin and over two thousand analogues have been synthesized and tested for antitumor activity (132).

4.3. Use

The use of platinum metal and its alloys in industry is mainly related to their extraordinary catalytic properties. As a catalyst platinum is used in hydrogenation, dehydrogenation, isomerization, cyclization, dehydration, dehalogenation, and oxidation reactions (12, 90). One of its major industrial uses is in the oil industry. The metal is dispersed on small pellets of alumina or silica-alumina and used to upgrade the octane rating of gasoline (12, 108). In the chemical industry platinum-rhodium alloys are used in catalyst gauzes for ammonia oxidation during the production of nitric acid. Platinum catalysts may also be used e.g. in a process for making sulfuric acid (12, 108). Ceramic honeycomb materials impregnated with platinum are used in industry for exhaust-gas control (108). Platinum-rhodium or platinum-palladium catalysts are used to control emissions from automobile exhausts and oxidizes carbon monoxide and unburnt hydrocarbons and in the case of Pt-Rh reduces nitrogen oxides (22, 63).

Resistance to many forms of corrosion and strength at high temperatures are other important properties of platinum and it is often alloyed with other platinum metals or base metals and used in electric contacts, circuits printed onto ceramic substrates (in the electronics industry), laboratory and plant apparatus, electrochemical anodes, spinnerets used for synthetic fiber extrusion, bushings for the production of fiberglass and vessels used for example in glass-making industry. Platinum is also used to produce a silvery lustre on ceramic glazes (12, 22, 63, 90, 108). Some alloys containing platinum are used in dentistry and in surgical tools and implants. Another well-known use of platinum and its alloys are in jewellery (12, 63).

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 platinizing alumina or charcoal in catalyst production (59, 63). A number of salts can be used in the electrodeposition of platinum. Industrial items (e.g. aviation components, electrodes, turbine blades, wire), as well as jewellery and decorative items may be electroplated with platinum. Established processes are based on materials such as diamminedinitroplatinum(II), sodium hexahydroxyplatinate(IV), potassium hexahydroxyplatinate(IV), hexahydroxyplatinic acid(IV), hexachloroplatinic(IV) acid or dinitrosulphatoplatinous(II) acid (potassium dinitrosulphatoplatinate(II), potassium dinitrodichloroplatinate(II) or potassium trinitrochloroplatinate(II) are used for making up solutions), but electrolytes based on chlorides (basic salts: platinum(IV) chloride, ammonium hexachloroplatinate(IV), hexachloroplatinic(IV) acid) have no great significance today. New series of aqueous platinum electroplating baths based on tetraammineplatinum(II) compounds are developing (10, 150). 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 (59, 90, 180). Potassium tetrachloroplatinate(II) possibly also may be used as a dental drug (dentine desensitizer) (72). Certain platinum complexes, like cisplatin and its analogues are used as anticancer drugs.

The demand for platinum has increased worldwide during the last twenty years mainly because of the introduction of the automobile exhaust gas catalysts (Table 3). Before that most of the platinum was used as catalysts in the chemical and petroleum industry. In Sweden the largest amounts of platinum still are used in the petroleum industry (Table 4). According to Statistics Sweden (SCB) at least 2-2.5 tons of platinum (for different purposes) was imported in Sweden in 1993. Secondary sources of platinum may come from recycling of used equipment. In Norway 151 kg of platinum (rough, semi-manufacture, pulverous) was imported and 1921 kg was exported in 1994 (Statistics Norway).

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) (Tables 4 and 5). A solution of hexachloroplatinic(IV) acid and rhodium chloride is used in the manufacture of car catalysts (Tables 4 and 5). Platinum complexes have been reported to be added as catalysts in products used for example for coating in the textile industry (Table 5) and to occur in products used for moulding in electronics plants (Table 5). Platinum also might be used in Sweden e.g. in jewellery, but there are no reliable figures on the amounts used for those purposes. Certain platinum compounds are used as cytostatic agents (cisplatin and carboplatin), while platinum and hexachloroplatinic(IV) acid have been reported to occur in homeopathic drugs (Swedish National Chemical Inspectorate).

Smaller amounts of platinum and platinum compounds are used in industry in Denmark (Table 6). According to the Danish Product Register platinum metal is used in small concentrations in solder paste/welding materials and conductor paste in the electroindustry, but the use of metallic platinum generally is not reported to the register and thus platinum may be used in other industries as well. Potassium hexachloroplatinate(IV) is used as a laboratory chemical and in very small concent-

Table 3. Platinum sales to various types of industry in the USA before and after the introduction of automobile catalytic converters (from 63)

Industry	1973		1987	
	kg/year	% of total	kg/year	% of total
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

Table 4. Major uses of platinum and platinum compounds in industry in Sweden in 1993*

Industry	kg	Compound
Petroleum	3050	Platinum
Chemical	67	Platinum(II)oxide, platinum(II)sulphide, platinum
Metal finishing	250	Hexachloroplatinic acid

*Figures according to the product register from the Swedish National Chemical Inspectorate.

Table 5. Amount of platinum/platinum compounds in different products* used in industry in Sweden in 1993

Function	Compound	Number of products	Conc (%)	Total amount (kg)
Catalyst	Platinum	4	<2	<3055
Raw material	Hexachloroplatinic acid	1	25	250
Catalyst	Platinum(II) oxide	1	<1	<32
Catalyst	Platinum(II) sulphide	1	<1	<32
Catalyst	Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes	1	4	4
Catalyst	Platinum, chlorooctanol complexes	2	<0.2	<0.8

*Figures according to the product register from the Swedish National Chemical Inspectorate.

Table 6. Amount of platinum/platinum compounds in different products* used in industry in Denmark in 1992

Function	Compound	Number of products	Conc. (%)	Total amount (kg)
Not given	Platinum	25	-	2-3
Not given	Potassium hexachloroplatinate	3	-	1-2
Catalyst	Hexachloroplatinic acid	5	-	<1
Catalyst	Hexachloroplatinic acid hexahydrate	2	-	<1
Catalyst	Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes	6	-	<1
Catalyst	Platinum, carbonyl chloro 2,4,6,8-tetraethenyl-2,4,6,8-tetramethyl-cyclotetrasiloxane complexes	3	-	<1
Catalyst	Platinum, chlorooctanol complexes	1	-	<1

*Figures according to the Danish Product Register.

rations in heating, water and sanitation products. Hexachloroplatinic(IV) acid and different complexes of platinum are used in very small concentrations as catalysts in raw materials used in the chemical industry and in silicon-based lubricant stuff and polishing material used in the iron/metal industry and wood/furniture industry (personal communication, O. M. Poulsen, National Institute of Occupational Health, Denmark).

In Norway platinum metal, hexachloroplatinic(IV) acid, platinum(II) oxide, platinum(IV) oxide and an unspecified platinum complex are registered in the Product Register (1996), but statistics on the amounts used are only available for hexachloroplatinic(IV) acid (14 products) and the unspecified platinum complex (1 product). These two platinum compounds are used in very small amounts mainly in varnish and other products used for painting and constitute totally <<500 kg. The products are used e.g. in chemical-technical industry, aircraft industry, during building/constructing and for private use (personal communication, P. Kristensen, National Institute of Occupational Health, Norway).

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 tetraammineplatinum hydrogencarbonate is used by a manufacturer of automobile catalyzers (personal communication, V. Riihimäki, Finnish Institute of Occupational Health).

5. Occupational exposure

There are three primary categories of industrial sources for exposure to platinum: mining, refining and processing. Platinum in the mining operation usually is found in the insoluble form, as the free metal or in other forms which are very insoluble (66). The refining operations provide the possible exposure of predominantly the soluble forms of platinum, especially during the latter steps and the chief occupational exposure to chloroplatinic acid/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, that is when platinum is reclaimed from scrap metal and expended catalysts (including automobile exhaust catalysts and catalysts used e.g in the oil refining industry) (7, 13, 27, 66, 120, 124). However, occupational exposure to hexachloroplatinic(IV) acid or platinum salts also might be expected e.g. in the manufacture of emission control systems for cars and catalysts for agricultural fertilizers, at small-scale plating or coating operations, during laboratory handling and in the photographic industry (10, 42, 56, 90, 119, 150, 180). Exposure to certain platinum compounds (antineoplastic drugs) also might occur in hospitals (34).

There is some information available regarding platinum levels in the work environment (Table 7), but the exposure data may not be directly comparable due to differences in sampling and analytical techniques etc. The contribution of soluble platinum salts to the content of platinum in the atmosphere also is very different.

Few data concerning air levels of platinum in mines have been published. In one study (65) air samples were collected from the mines in the Sudbury area in Canada, during underground mining and in the building where the metals were removed from the crushed ore slurry. The platinum levels generally were found to be below the detection limit (<0.003 $\mu g/m^3$), except in the precious metals area where the air level of platinum was 0.377 $\mu g/m^3$. However, the ore contained very low levels of Pt as compared with South African ore which was 10-20 times higher.

In platinum refineries the air levels of platinum have been found to be very variable. Extremely high levels of platinum (5-80 mg/m^3) were reported in a badly ventilated platinum refinery in China, where the workers were exposed to dust or spray of complex platinum salts and platinum metal. The average concentration at most points was below 10 mg/m^3 (149). In an American study (65) the platinum concentration in air in a typical refinery in New Jersey was found to be between 0.02-0.26 $\mu g/m^3$ (mean: 0.16 $\mu g/m^3$) in the refinery section and 0.13-0.21 $\mu g/m^3$ (mean: 0.18 $\mu g/m^3$) in the salts section (sampling for 5 days). In two late German studies the air levels of platinum also were stated to be very low. In one study (21) it was stated that 2.0 $\mu g/m^3$ was maintained over the long term, but two stationary air monitorings of total dust in the separation shop in 1986 for 2 h showed concentrations of platinum salts of 0.08 and 0.1 $\mu g/m^3$. Two personal air monitorings in filter press workers for 1 h showed levels <0.05 $\mu g/m^3$ (detection limit). Processes considered to have relatively low or moderate exposure to platinum were e.g. alkaline dissolution of metallic platinum and manufacture of catalysts, while relatively high

Table 7. Workplace concentrations of platinum in various types of industries

Industry	Process, work operation	Concentration	Ref
Mine	mine, furnace room precious metals area	<0.003 μg/m^3 0.377 μg/m^3	65
Platinum refinery	refining of platinum-iridium alloy	5000-80000 μg/m^3	149
Platinum refinery	crushing $(NH_4)_2(PtCl_6)$ discharging $(NH_4)_2(PtCl_6)$ fr ovens sieving platinum metal neutralizing platinum salts other areas	<1700 μg/m^3 >68 μg/m^3 400-960 μg/m^3 18-20 μg/m^3 0.9-9.5 μg/m^3	37,59
Platinum refinery	salts section refinery section	0.13-0.21 μg/m^3 0.02-0.26 μg/m^3	65
Platinum refinery	generally	<0.08 μg/m^3	95
Platinum refinery	separation shop generally	0.08, 0.1 μg/m^3 <2.0 μg/m^3	21
Platinum refinery	refining, catalyst manufacture handling and dispensing of solids and solutions	<2 μg/m^3 <16 μg/m^3	56
Platinum recycling industry	recovery refinery warehouse analytical laboratories other areas	2.7, 5.3 μg/m^3 10.7, 27.1 μg/m^3 8.6 μg/m^3 0.4 μg/m^3 0.5, 0.6 μg/m^3	7
Precious catalysts reprocessing plant	destruction of spent catalysts	40 - 240 μg/m^3	47
Platinum recycling industry	cutting cutting draining draining generally	15 μg/m^3 10 μg/m^3 (in resp. dust) 71 μg/m^3 24 μg/m^3 (in resp. dust) <1 μg/m^3	*
Platinum metal using industry	production of catalysts grinding, polishing, cutting, sawing recycling of platinum catalysts	0.3-19.9 μg/m^3 1.8-3.1 μg/m^3 3.8 μg/m^3	139
Car catalyst manufacturing	dilution of hexachloroplatinic acid, coating of catalysts, packing area, lab work	<0.4 μg/m^3	42
Manufacture of platinum-coated oxygen sensors		0.14-1.83 μg/m^3	56,148

*Gerd Sällsten, department of occupational medicine, Gothenburg, Sweden, personal communication 1996.

exposure was found in the platinum refinery (no more details known). In the second study (95) platinum salt exposure in the different working areas had been measured by the refinery and was generally below 0.08 μg/m^3. However, the exposure during the drying process of the salts was considered as too high. No further details on the measurements were available. In a report from 1945, four British refineries were investigated and estimations of the air levels of platinum were made at different sampling points (37, 59). Air levels of less than 5 μg Pt/m^3 were found in the majority of the refining operations (wet processes and/or local exhaust ventilation), but levels up to 1700 μg/m^3 were measured e.g. during crushing of ammonium hexachloroplatinate(IV).

A recent document from the UK (56) stated, regarding exposure to soluble platinum salts, that about 96% of 8-hour TWA exposure measurements at refining and catalyst manufacture were well below 2 μg/m^3 (calculated from measurements of exposure not available). The majority of exposures above this value occurred during the production and dispensing of soluble platinum salts. However, there was a higher percentage of results (10%) above 2 μg/m^3, when the results were looked at without reference to time-weighing and data relating to exposures of 1 to 4 hours indicated numerical values up to 7 to 8 times the occupational exposure limit value of 2 μg/m^3 for the duration of the sampling period. There was also a wider range of production areas which gave rise to these results, including process catalyst production, platinum recovery, platinum refining.

In an investigation in the USA, the air levels of platinum salts were measured in 1977-1979 (>75 air measurements), in a plant, that reclaimed platinum and other precious metals from scrap metals and expended catalysts. Elevated platinum salt air measurements were noted in the recovery, refinery and warehouse areas and the mean air concentration (TWA 8 hr) often exceeded 2 μg/m^3. It was estimated that within a four-month period of measurements this value was exceeded between 50 and 75% of the time (7, 23). In an unpublished Swedish report (Gerd Sällsten, personal communication 1996), platinum air levels between 15 and 71 μg/m^3 was found by personal sampling (197-305 min) in one worker during recycling of platinum catalysts. The Pt air levels were stated to be below 1 μg/m^3 for the other few workers. The exposure of workers to metallic catalyst dust was assessed in a French study (47). In most instances other metals than platinum were measured, but personal exposure of platinum for one worker at a precious catalysts reprocessing plant, where metals were recovered by the destruction of spent catalysts, was reported to be between 40 and 240 μg/m^3 (sampling for 3 days). The concentration of total platinum in air in the platinum metal using industry, determined by stationary and personal sampling at several working sites (no details were given), was reported in another study (139) to range 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, sawing) of platinum containing materials. A median value obtained in plants used for recycling of platinum catalysts was 3.8 μg/m^3.

The exposure to platinum during manufacturing of car catalysts was investigated in a Swedish study (42). A solution containing hexachloroplatinic(IV) acid and

rhodium chloride (5:1) was used in the factory for the production of catalysts. Personal sampling was undertaken e.g. during preparation of the platinum/rhodium solution, analytical work, work in the box used for coating of catalysts, and during packing of catalysts. The Pt values were found to be <0.2 μg/m^3 (below detection limit). When stationary sampling was used the air levels of platinum were given as <0.4 μg/m^3 during dilution of the platinum/rhodium solution and <0.2 μg/m^3 during coating with the platinum/rhodium solution and in the packing area.

In a Japanese study (56, 148) the concentrations of platinum in the air during the manufacture of platinum-coated oxygen sensors was measured. 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. Measurements of the concentrations of Pt in the air at the two electrodes ranged from 0.14 to 1.83 μg/m^3 with 48-hour averages of 0.46 and 1.1 μg/m^3. Cleaning of the sensors was stated to involve exposure to fine dust of ammonium hexachloroplatinate(IV) at higher concentrations than those in the workplace as a whole, but no quantitative values were given in the study.

6. Sampling and analysis

One important method (MDHS 46) for determination of platinum metal and soluble inorganic salts of platinum in air has been developed by the UK Health and Safety Executive (22, 56). Air is drawn for two hours through a mixed-cellulose ester filter, which is then treated with hydrochloric acid to dissolve soluble platinum salts. The resultant solution is analyzed for platinum by graphite furnace atomic absorption spectrometry (GFAAS) at a wavelength of 265.9 nm. Platinum metal and insoluble salts are determined by dissolution in 50% aqua regia followed by evaporation to dryness several times with concentrated hydrochloric acid before proceeding as before. Another method (S191), enabling the determination of soluble platinum salts and platinum metal together with insoluble platinum salts, has been produced by the US National Institute for Occupational Safety and Health (110). The aerosol fraction is collected on a mixed cellulose ester filter which is then wet-ashed using nitric acid to dissolve the organic matrix. Soluble platinum salts are taken up in a nitric/perchloric acid solution and platinum metal and insoluble platinum salts are dissolved in a nitric/hydrochloric acid solution. The resultant solutions are analysed for platinum by GFAAS. The method has been validated with potassium hexachloroplatinate(IV) over the range of 0.00079-0.0031 mg/m^3 using a 720 L sample. The detection limit of the method (720 L sample) was 0.00014 mg/m^3 (110).

Other methods for determination of platinum in air has been described more recently by NIOSH (111) and OSHA (116). These methods according to HSE (56), determine only total platinum and use analytical techniques (inductively coupled plasma atomic emission spectrometry (ICP-AES), flame atomic absorption spectrometry (FAAS)) with a relatively poor detection limit for platinum in comparison to

GFAAS. However, none of the above mentioned methods may be suitable for determination of short-term activity-related exposure if the platinum concentration in air is low. Sample solutions may then be analysed by inductively coupled plasma mass spectrometry (ICP-MS), a technique which exhibits a significantly lower detection limit for platinum than GFAAS (56). For further details on different methods for determination of platinum and its salts in workplace air e.g. see references 56 and 63.

Several techniques have been used to determine platinum levels in biological samples (114). When flameless AAS was used for measurement of platinum in tissues, the practical limit of the assay in one study (128) was estimated to be about 0.1 μg/g wet tissue (1-g tissue sample). Direct analysis allowed for determination of as little as 0.02 μg Pt/g plasma (0.2-0.5 ml blood samples) (128). Other, more sensitive methods enabling the determination of Pt at the μg/g to pg/g levels also have been developed (11). One method based on adsorptive voltammetry (AV) is extremely sensitive and is considered to allow a reliable determination of baseline platinum levels (139). A detection limit for this method down to 0.2 ng Pt/L for urine (sample volume: 10 ml) and 0.8 ng Pt/L for blood/blood plasma (samle volume: 3 ml) has been reported (96). The detection limit for platinum in blood, when an AV method was used by Nygren et al (114), was 0.017 μg/L (100 ul sample). Radiochemical neutron activation analysis (RNAA) and ICP-MS are other methods for determining traces of platinum (63, 96, 98). For ICP-MS the limit of detection is in the order of 0.01 μg/L (164). A good correlation between ICP-MS and AV was shown in a study by Nygren et al (114). Currently there are no external quality assessment schemes for analysis of platinum in biological fluids. Suitable standards for internal quality control have according to HSE been identified from the National Bureau of Standards (USA) as spiked and normal urine (56).

7. Toxicokinetics

7.1 Uptake

The uptake of platinum compounds is dependent on the physicochemical properties of the compound and the route of administration.

In general deposits of insoluble metallic compounds in the airways are more likely to be cleared by the mucociliary apparatus, while soluble metallic salts may readily dissociate and be transported as metal ions into lung tissues (13). However, no quantitative data concerning absorption of platinum compounds via the lungs have been found. Excretion data on male rat (Charles River CD-1) indicated that most of the inhaled particles (5-8 mg/m^3; 48 min) of platinum metal, platinum(IV) oxide, platinum(IV) sulphate (1.0 μm) and platinum(IV) chloride (1.0 μm) was cleared from the lungs by mucociliary action, swallowed and excreted via the faeces (101). The presence of ^{191}Pt in the blood (counted only after exposure to platinum metal) and the urine indicated the absorption of a small fraction of ^{191}Pt, although it was impossible to determine the relative contributions of lung and of gastrointestinal

Table 8. Percentage of initial lung burden retained with time in the lungs (from 101)

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	28.0	17.9	4.4

absorption to the total body burden (101). Retention data (Table 8) for platinum(IV) sulphate, platinum metal and platinum(IV) oxide indicated, that the water-soluble compound (platinum(IV) sulphate) was more rapidly mobilized from the lung than the other two compounds.

Gastrointestinal absorption has been studied to some extent in animal experiments. In one study (99, 100) less than 1% of the initial dose (25 μCi) was roughly calculated (whole-body retention data) to have been absorbed through the gastrointestinal tract in rat after a single administration of platinum(IV) chloride. In another study (19) platinum metal or platinum(IV) chloride was given in the diet in five different concentrations to female rat from four weeks before pregnancy to the twentieth day of gestation. A much better uptake, reflected as a higher concentration of platinum in blood and selected tissues was found for the water-soluble salt, but the total amount absorbed through the gastrointestinal tract (not given) seemed to be small. Other data concerning blood levels of Pt and organ distribution of Pt in small rodents after administration of platinum compounds (e.g. 50, 85) also show peroral absorption, but no percentages are given. Peroral uptake of Pt probably is dependent i.a. on the particle size, since in one study on platinum metal (6), administration of smaller particles (0.5 μm) led to a higher Pt retention, than larger particles (150 μm).

In contrast to the limited experimental data indicating a small peroral uptake of platinum and soluble salts of platinum, excretion data in a study on humans showed a large peroral uptake of platinum (168). When the amount of Pt excreted in urine during 24 h was measured it 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 required to make more reliable conclusions on uptake.

No quantitative data on skin resorption have been found, but in a Russian study (133) dermal application of ammonium chloroplatinate (and a palladium compound) was reported to be accompanied by reduced body-mass gain in the experimental animals (species not given). After termination of the experiment platinum was found in all internal organs examined as well as in urine and blood. No further details of the study are given, and e.g. the contribution of peroral uptake cannot be excluded. In a skin sensitisation study on guinea pigs and rabbits for US 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, thus suggesting little or no dermal absorption of this platinum salt (157). However, the platinum level in spleen was assessed about 14 days after the last application of platinum paste (and after the skin test procedure).

7.2 Distribution

In vitro studies have shown that ammonium tetrachloroplatinate(II) and potassium tetrachloroplatinate(II) bind to serum albumin and transferrin (40, 156, 165). 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 (168). Erythrocytes were also found to contain more platinum (platinum(IV) chloride, platinum metal given perorally) than plasma in a study (19) in rat (Sprague-Dawley, females).

The route of administration is important in determining the retention of platinum. In studies in male rat (Charles River CD-1) the whole-body retention of ^{191}Pt (platinum(IV) chloride; single exposure) has been shown to decrease in the following manner: intravenous > intratracheal > inhalation > oral (99, 100, 101). There is a time differential in the attainment of maximum Pt levels among different organs/tissues and the distribution of platinum compounds also changes with dose, but generally the greatest accumulation after absorption has been shown in the kidney (6, 19, 50, 85, 99, 100, 101, 130).

Experiments with labelled platinum(IV) chloride showed that after intravenous dosing (25 μCi) to rats, radioactivity was found in all the tissues analyzed. The concentrations were higher than in the blood, during the first 7 days after exposure, in the liver, spleen, adrenal gland and kidney, whereas low levels were found e.g. in fat. The large amount of radioactivity found in the kidney (day 1: 6.7% per gram; day 14: 1.2% per gram) suggested that this organ accumulated ^{191}Pt. The lowest amount of radioactivity was found in the brain, indicating that ^{191}Pt was transferred only to a limited extent through the blood-brain barrier (99, 100). The percentage of absorbed dose in liver, muscle, kidney, blood and bone, one day after an intravenous administration of labelled sodium tetrachloroplatinate(II) (dose not given), was reported in another study in rat (female albino) and constituted about 13, 12, 10, 7 and 6%, respectively. It was also stated (no details were given) that decrease in tissue content of Pt roughly paralleled the decline of the blood concentrations and that Pt was easily measurable in the blood as long as 32 days after injection (33).

Exposure to platinum compounds through inhalation has been found to lead to an accumulation in the gastrointestinal and respiratory tract immediately after exposure. In a study in male rat (Charles River CD-1) with ^{191}platinum metal or ^{191}platinum oxide (7-8 mg/m^3; 48 min; particle size not given) it was shown, that the initial lung burdens for ^{191}Pt metal and ^{191}platinum oxide represented about 14% and 16% of the initial body burdens (101). Most of the radioactivity had been eliminated from the gastrointestinal tract within 24 h, while the lung still contained about 60% of the initial lung burden (Table 8). In addition to the lungs and trachea, the kidney and bone was found to contain the highest concentrations of radioactivity (platinum

Table 9. Radioactive ^{191}Pt in selected tissues following inhalation exposure to Pt metal (from 101)

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

metal) when ^{191}Pt was counted in selected tissues 1-8 days after exposure (Table 9). The brain contained very small amounts of ^{191}Pt (101).

Peroral administration to rat has shown, that administration of a water-soluble salt such as platinum(IV) chloride lead 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 Pt metal, especially in the kidneys (6, 19). In these and other animal experiments the absorbed Pt has been shown to be generally distributed and usually the highest amounts of Pt (platinum metal, platinum(II) chloride, platinum(IV) chloride or platinum(IV) sulphate) have been found in the kidney, while low levels have been found in adipose tissue and brain (5, 6, 19, 50, 85, 99, 100, 130).

Foetal uptake of platinum compounds has been investigated in a few studies and found to be very low. In one study (99) rats were given 25 μCi ^{191}platinum(IV) chloride intravenously and were killed 24 h later. Very small amounts of ^{191}Pt were present in all the foetuses counted and averaged 0.01% of the dose/g in whole foetal tissue and 0.05% of the dose/g in foetal liver. Placental levels were relatively high (0.92% of the dose/g) and only the maternal liver (1.44% of the dose/g) and maternal kidney (4.22% of the dose/g) had higher concentrations than the placenta (99). In an unpublished study in mice (88) it was found, that placental Pt levels were greater than blood levels (most obvious a few days after administration) when sodium hexachloroplatinate(IV) was administered subcutaneously at the LD_1 level (22 ppm (mg/kg bw) Pt) on days 7 or 12 of gestation. The Pt levels in foetus and in the suckling offspring of dams receiving a single dose of sodium hexachloroplatinate(IV) day 2 post partum were low. In another study in rat (76) platinum(IV) chloride or platinum metal was given in the diet in five different concentrations (up to 100 mg/kg diet) from four weeks before pregnancy to the twentieth day of gestation. The concentration of Pt in uterus and in the foeto-placental unit generally was much higher in the platinum(IV) chloride groups than in the corresponding platinum

metal groups, but still constituted a very small part (e.g. <=0.006% in amnion) of the ingested amount of Pt. The highest Pt concentration (both compounds) in the foeto-placental unit was found in amnion, where about 80-90% of the measured platinum was situated. The lowest Pt content was found in the foetus (above the detection limit only in the 50 and 100 mg/kg groups given platinum(IV) chloride). When platinum(IV) chloride or platinum(II) chloride was given in concentrations up to 100 mg/kg diet to lactating rats only platinum(IV) chloride was detected in the milk (at the 50 and 100 mg/kg level), but platinum could be determined in the carcass of the offspring after administration of platinum(IV) chloride as well as platinum(II) chloride (at the 50 and 100 mg/kg levels). The level of Pt in the offspring was found to be highest at the end of the lactation period and generally the platinum content was higher in the offspring after administration of platinum(IV) chloride (77).

Human tissue burden of platinum was determined in 1313 samples (97 individuals) through autopsy tissue analysis in California in 1974-1975, when catalytic converters still were uncommon (32). In 46% of the individuals Pt was detected in one or more tissues (about 5% of the samples). The range of the platinum concentrations detected was 3 to 1460 ng/g wet tissue. Tissues in which the highest concentrations of platinum were found were, in descending order: subcutaneous fat, kidney, pancreas, and liver (32). One sample out of nine analysed showed the presence Pt in the brain. The presence of platinum in subcutaneous fat was surprising. Conversion of lipid-insoluble platinum compounds to lipid-soluble compounds e.g through methylation possibly could be an explanation, but the analytical accuracy has been questioned and contamination of the samples suspected. When analysis of platinum content in autopsy tissue samples (liver, kidney, spleen, lung, muscle, fat) from 10 people in California (1974) were made by another laboratory, the concentrations of Pt were determined to be considerably lower and below the limit of detection for all the samples (e.g. <3 ng/g (<2.6 ppb) wet tissue in the kidney) (65). The platinum level in tissues of about 40 persons with no known occupational exposure to metals was also determined in a late Japanese study (181). The platinum levels were found to be up to 1170 ng/g wet weight in liver and decreased in the following order: liver, kidney cortex (<330 ng/g), spleen (<320 ng/g), heart (<316 ng/g), and kidney medulla (<145 ng/g)), but platinum was detected only in a few persons. In the brain (cerebrum, cerebellum) none of the samples were above the lower limit of determination (27 ng/g wet weight) (181). In contrast, the platinum level in liver (11 samples from 1980) in another study in human was very low: from 0.005 to 0.057 ng/g wet weight (183). The Pt level in human heart (n=9), determined in a Swedish study (175), was 0.5-1.2 ng/g wet tissue. In one study (65) the results of analysis of tissue samples from nine individuals previously employed by mining and ore processing plants in Canada were presented, and it was shown that detectable concentrations of platinum only were found in three samples (lung: 3.7 ng/g (ppb), fat: 4.5 ng/g (ppb), muscle: 25 ng/g (ppb)).

7.3. Elimination

Excretion, following intravenous administration to male rat (Charles River CD-1) of labelled platinum(IV) chloride, was shown in one study (100) to occur both in the urine and faeces, but the urine contained a greater quantity of radioactivity. The whole-body retention after three days was 65% and after 28 days about 14%. In another study in rats (female albino) about 40% of an injected dose of labelled sodium tetrachloroplatinate(II) was stated to have been eliminated in urine and faeces in 24 h and 92% in 32 days (33). When ^{191}platinum(IV) chloride was administered perorally to male rat (Charles River CD-1) most of the ^{191}Pt was eliminated in the faeces and only a small amount was excreted in the urine. This was probably due to passage of unabsorbed ^{191}Pt through the gastrointestinal tract and was in accordance with the rapid decline of the whole-body retention curve to less than 1% at the end of three days (99, 100).

Radioactivity in the urine and faeces samples from rats (males; Charles River CD-1) following inhalation exposure for 48 minutes to particulates of 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) pointed to that most of the ^{191}Pt was eliminated in the faeces during the first days. However, there were small amounts of radioactivity present in the urine too (101). Whole-body retention curves showed an initial rapid clearance of ^{191}Pt from the body followed by a slower clearance phase during the remainder of the post-exposure period. The whole-body retention of ^{191}Pt measured as a percentage of the initial body burden 24 h after exposure to platinum(IV) chloride, platinum(IV) sulphate, platinum(IV) oxide and platinum metal was 41, 33, 31, and 20%, respectively. After 10 days around 7-8% of the initial ^{191}Pt was retained, except after inhalation of platinum(IV) chloride where only about 1% was retained (101). The clearance of ^{191}Pt from the lungs also could be divided into an initial rapid phase (24 h) and a later slow phase. For the slow phase, the clearance half-time was about eight days (101).

Excretion in human has been estimated to some extent and limited data point to a slow elimination of platinum metal. In one study (4) no obvious difference of the platinum content before and after an exposure-free period (15 days) could be shown, when platinum was measured in the urine (and serum) of four workers occupationally exposed to platinum metal. In concordance with this, increased urinary values of Pt was found in one worker exposed to platinum during recycling of platinum catalysts (cutting, draining), while no definite decrease in urinary levels of platinum was seen during an unexposed period (at least 12 days) (Gerd Sällsten, personal communication). The urinary excretion of platinum was estimated in one adult male from Sydney (with no occupational exposure of platinum compounds) and found to be between 0.76 and 1.07 μg/day (168). However, the values obtained in this study are very high compared to the values of Pt content in urine obtained by some other authors (see Section 8 Biological Monitoring).

8. Biological monitoring

Reference values of platinum in blood and urine have been estimated in some studies in recent years, but there are large discrepancies in the results obtained by different authors. In an Australian study (168) baseline levels of platinum in the blood, hair and urine were determined by a method based on AV. The mean concentrations of platinum in samples from residents (n=21) in Sydney were 0.60 μg/L (range 0.09-1.72 μg/L) in whole blood, 4.90 μg/kg (range 0.87-18.31 μg/kg) in hair and 0.33 μg/g creatinine (range 0.03-0.82 μg/g creatinine) or 0.25 μg/L (range 0.02-0.92 μg/L) in urine. No relationships between the platinum levels in blood, hair and urine were observed and no differences between samples obtained from Sydney and from a relatively unpolluted area in Australia were found. As another part of this study the level of platinum in blood was measured in subjects from Umeå in Sweden (n=10), and the blood levels were found to be about the same as in Australia (mean, 0.58 μg/L, range 0.12-1.58 μg/L) (113). In an earlier study (114) the natural levels of platinum determined by AV in human blood (n=18) and urine (n=11) were found to be in the range of 0.1-2.8 μg/L (median 0.59 μg/L) and 0.04-0.61 μg/L (median 0.11 μg/L), respectively. The levels of platinum in blood in the above mentioned studies were close to the levels (determined by AAS) found in 750 ml composite blood samples collected in USA in 1974, when few car catalysts were used. The blood levels of platinum obtained from a population living near a heavily travelled urban freeway in Los Angeles, California and from a population in the high desert area were 0.49 μg/L and 1.80 μg/L, respectively (67).

In a recent German study (96) "normal" values for platinum in blood (n=13) and urine (n=14) determined by a method based on AV were much lower, than in the above mentioned studies, and ranged from <=0.8 to 6.9 ng/L in whole blood or plasma and 0.5 to 14.3 ng/L (mean 3.5 ng/L) in urine. It was also stated, that a significant correlation was evaluated for the relationship between the platinum levels in blood, serum and urine (139). The higher baseline levels obtained by Nygren, Vaughan et al (113, 114, 168) were not considered by these authors (96, 139) to correspond to the concentrations of platinum in the earth´s crust, but no explanation for the differences was given. When blood samples from three persons not occupationally exposed to platinum was collected in Sweden in 1993, and some of these samples were analyzed in laboratories in Umeå (Sweden) and Dortmund (Germany) by the same method (AV) and in Lund (Sweden) by a different method (ICP-MS), the results were found to differ greatly, even though the same tubes for blood sampling had been used (Gerd Sällsten, personal communication). The single value obtained from Lund and the values obtained from the German laboratory were much lower than the corresponding Umeå values. Furthermore, there were rather large fluctuations in some of the values obtained from Umeå. These data further support the assumption that the correct base value in blood is very low - in the order of some nanogrammes per litre. The Pt level in urine of one control subject also was determined (ICP-MS; Lund) and found to be 10-30 ng/L (Gerd Sällsten, personal

communication). In a recent study concerning exposure to platinum-containing antineoplastic drugs in hospital pharmacy personnel and nurses (34), the mean urinary platinum level in controls (n=11) (determined by voltammetric analysis after UV photolysis) was 5.3 ng/L (range 2.1-15.2 ng/L or 2.3-10.4 ng/g creatinine).

Some studies have shown elevated levels of platinum in blood or urine (compared to control subjects) in occupationally exposed persons. In one study (139) the platinum levels were determined by AV for 40 employees exposed to metallic platinum during manufacturing and recycling of platinum containing catalysts or mechanical treatment of platinum containing materials (no data concerning exposure time were given). The platinum levels of the exposed workers were elevated and ranged from 10-9200 ng/L in urine (mean values: 1260 ng/L-production; 330 ng/L-recycling; 429 ng/L-mechanical treatment), 2-180 ng/L in blood (mean values: 39 ng/L-production; 125 ng/L-mechanical treatment) and 4-280 ng/L in serum (mean values: 39 ng/L-production; 75 ng/L-mechanical treatment). A significant correlation was evaluated for the relationship between the platinum levels in blood, serum and urine, but no significant relationship could be found between the ambient air platinum levels and the concentrations in blood, serum and urine. Ranges for platinum concentrations in air were 0.3-19.9 $\mu g/m^3$ (median 3.1 $\mu g/m^3$) during production of catalysts and 1.8-3.1 $\mu g/m^3$ (median 1.8 $\mu g/m^3$) during mechanical treatment. A median value for recycling was also given: 3.8 $\mu g/m^3$ (139). Similar values were presented in another study published by the same authors (96), but there are some discrepancies in the lower range values of urine, blood and plasma of exposed persons as well as in the number of samples. In a pilot study (173), probably part of the above mentioned German studies, platinum levels in urine for 21 exposed men were 20-630 ng/L (median 320) during recycling, 70-1350 ng/L (median 280) during processing and 10-2900 ng/L (median 330) during mechanical treatment. The values for platinum levels in blood and serum were between 100 and 280 ng/L and the air levels of platinum between 1.7-6.0 $\mu g/m^3$. However, in this work it was stated, that a significant correlation between blood/serum platinum levels and air platinum levels was apparent, whereas no significant correlation between blood and urine was found. In an unpublished Swedish report (Gerd Sällsten, personal communication) the urinary concentration of Pt in one worker, measured by ICP-MS, exposed to total platinum air levels between 15-71 $\mu g/m^3$ during recycling of platinum catalysts (cutting, draining) was 150 ng/L.

In a study from the USA (14) sera of 12 current workers exposed to soluble platinum salts in a platinum refinery and three former workers (all 15 were skin-test positive) were analyzed by flameless AAS for Pt. Sera from eight persons had detectable levels of Pt (ranging from 150 to 440 ng/g (ppb)). The mean level of Pt in the sera of the current exposed workers was 240 ng/g (ppb). Pt concentrations in the sera of three terminated and four presently employed workers were at or below the lower limit of detection by this method. No measurements of the air levels of platinum were presented. When samples of blood and urine were collected from refinery workers (n=61) at a refinery in New Jersey, the levels of platinum in blood were below the detection limit (<1.4 ng/g (ppb)), whereas about 10% of the urine samples (6/58) had measurable amounts of platinum (0.23-2.58 $\mu g/L$; detection

limit 0.1 μg/L). The air levels of platinum in the refinery section and the salts section were 0.02-0.26 μg/m^3 (mean: 0.16 μg/m^3) and 0.13-0.21 μg/m^3 (mean: 0.18 μg/m^3), respectively (65). The platinum content in urine in these areas were: 0.49 and 0.66 μg/L (refinery), and 1.22 and 1.24 μg/L (salts section). Samples of blood, urine, faeces and hair from 49 workers in mining and ore processing working in Canadian mines were also collected. It was found that the platinum content in all the samples were below the limits of detection (e.g. blood <0.0014 μg/g (ppm) in a 15 ml sample, urine <0.00002 μg/g (ppm) in a 1 L composite sample). Air samples collected during underground mining and in the building where the metals were removed from the crushed ore slurry generally also showed platinum levels below detectable levels (<0.003 μg/m^3), but in the precious metals area the platinum level was considerable higher: 0.377 μg/m^3 (65).

Due to analytical problems and difficulties in establishing a reference value for platinum in blood and urine no method can yet be used routinely for the monitoring of platinum. Methods based on AV are extremely sensitive, but must be further evaluated before they can be handled reliable in practice. Most other available analytical methods do not have the required sensitivity for monitoring of low levels of platinum in occupationally exposed workers.

9. Mechanisms of toxicity

Platinum salts may induce bronchoconstriction, anaphylactic shock and elevated plasma histamine levels in animals (monkey, dog, guinea-pig, rat) at the first contact and without any previous exposure to platinum salts, thus through pharmacologic or irritant mechanisms (17, 120, 136). In one study (136) it was shown, that an intravenous injection of 1-2 mg/kg sodium chloroplatinate in guinea-pigs was followed by bronchospasm as intense as if it was caused by the injection of 5 μg/kg of histamine dihydrochloride. A peculiarity was that the action of the chloroplatinate was exhausted after a few injections and the animal could resist a lethal dose of the salt. The previous injection of an antihistamine also protected the animal completely against the action of sodium chloroplatinate (120). The liberation of histamine from guinea-pig was reported by the authors (136) to be restricted to the chloroplatinate complex ($PtCl_6^{2-}$), whereas the chloroplatinite ($PtCl_4^{2-}$) was said to be devoid of this property both when tested in vitro and in vivo (20 mg/kg); however, no further details are given in the study. Other data, indicating that sodium hexachloroplatinate(IV) is a primary respiratory irritant producing bronchoconstriction was shown by Biagini et al (15). Pulmonary function was evaluated in a group of male Cynomolgus monkeys following acute serial bronchoprovocation challenges (inhalation of aerosol) using increasing concentrations of methacholine and a few weeks later sodium hexachloroplatinate(IV). The results showed (both compounds) concentration-dependent increases in mean values for pulmonary flow resistance (R_L) and decreases in dynamic compliance ($C_L$dyn), but the variation in results of R_L between individual animals was large. Concentration-dependent reductions were also found in maximal expiratory flow volume (MEFV) perfor-

mance parameters, and these data indicated that there were differential mechanisms of pharmacologic action for the bronchoconstrictive effects of the two compounds in monkeys.

However, in man the platinum salt-induced reactions of the respiratory tract and the skin generally is considered to be of immunologic origin, although the precise mechanism of sensitisation is still unclear (81, 94, 103, 118, 125, 144, 177). The symptoms appear to start after a sensitising period and only a fraction of exposed subjects become sensitised. Furthermore, the affected individuals become more and more sensitive to platinum and react to levels far below those normally encountered at work (17, 81, 95,120, 135, 136, 140, 177). Both atopic and nonatopic workers may be affected (23, 95, 115, 170) and smoking appears to predispose individuals to the development of platinum salts sensitisation after occupational exposure (7, 23, 84, 170). Tobacco smoke is believed to induce an increase in the permeability of the respiratory epithelium (7, 53, 184) and it has been proposed, that concurrent exposure to irritants (e.g. chlorine, ammonia, ozone) potentiate the effects of platinum salts exposure in the same way (7, 109).

An immunological reaction with platinum salts has been established in many cases in man by skin prick testing (type I reaction) with inorganic platinum salts (test sustances usually ammonium, sodium or potassium hexachloroplatinate(IV) or tetrachloroplatinate(II)), but sometimes pulmonary reactivity (expressed in bronchial provocation tests or as work-related symptoms) precede skin test reactivity or occur in workers with negative skin tests and there is a possibility that the initial pulmonary response is a sign of a hyperreactive pharmacologic effect rather than an immune effect. Otherwise there are different rates of dermatologic and pulmonary sensitisation (14, 15, 21, 23, 27, 29, 31, 58, 94, 95, 107, 115, 127, 129, 170, 177). There are other tests (mainly in vitro tests) indicating an IgE-mediated reaction too. However, the sensitivity and reliability of the skin prick test has not been equalled by any in vitro tests available (95, 135, 141). For example the presence of platinum salt-specific IgE antibodies in serum (exposed workers) has been demonstrated in vitro in radioallergosorbent tests (RAST)/ enzyme immunoassays (14, 21, 23, 29, 107, 125, 126, 182). A nonspecific immunopotentiation of an IgE response also has been proposed as a possible mechanism of sensitisation, since unusually high levels of total serum IgE has been noted in platinum metal refinery workers in many studies and atopic individuals usually have been eliminated during pre-employment screening in recent years (14, 21, 29, 95, 106, 107, 177).

In general, small molecular allergenic substances combine with large molecular carrier substances, mainly protein, to form complete antigens (act as haptens) which then can provoke a specific immune response. It has been shown in vitro, that platinum salts bind to e.g. serum albumin and transferrin, a major transport protein for several metal ions (27, 29, 38, 40, 156, 165, 177, 182), and probably the strength of the platinum-ligand bond, the reactivity of the complex towards protein or other carrier molecules and the ability of platinum to form stable complexes with e.g. proteins is of great importance for the allergenic potential of a platinum complex (1, 27). In a study in platinum refinery workers, known to be sensitive to hexachloro-

platinate or tetrachloroplatinate salts, a series of platinum complexes was used for skin prick tests (27). The results showed that the allergy-eliciting compounds only were confined to a small group of ionic complexes containing reactive halogen ligands. The chloroplatinates ($(PtCl_6)^{2-}$; $(PtCl_4)^{2-}$) were highly allergy eliciting and an allergenic response was obtained whenever at least one chloro ligand was present in a charged complex. The platinum(IV) and platinum(II) chloro species appeared to be equally effective possibly due to in vivo reduction of platinum(IV) to platinum(II). Changing from chloro to bromo ligands maintained the response but at an apparently reduced level. Neutral complexes and those containing more strongly bound ligands with poor leaving abilities were inactive immunologically, presumably due to little or no reaction with proteins. For example the leaving groups such as nitro- and thiocyanato- are much less reactive than the halogens and similarly the platinum amine linkage is very stable (27). However, antibody specificity factors may have played a role in the elicitation of reactions.

Platinum complexes preferentially bind to nitrogen and sulfur in proteins (108). The interaction with amino acids may lead to other effects than those depending on sensitisation e.g. reduced enzymatic activity (91). Inhibition of malate dehydrogenase, an enzyme active in the general metabolism, was shown in studies in vitro and the electrostatic charge of the platinum compound was found to be an important factor which influenced the degree of enzyme inhibition (162). The association constants were greatest for the dinegatively charged state, regardless of the valence state of the platinum, while there were no significant values for positively charged complex ions. Thus, $PtCl_4^{2-}$, $PtCl_6^{2-}$, $PtBr_6^{2-}$ and $PtBr_4^{2-}$ were most tightly bound to malate dehydrogenase in vitro and were strong enzyme inhibitors (39). In studies in vivo some dinegatively charged complex salts of platinum (K_2PtCl_4, K_2PtCl_6) have been shown to affect enzymes regulating the haeme pathway (see Section 10.7. Other Studies). Furthermore, in an in vitro study, potassium tetrachloroplatinate(II) was shown to weaken the interactions of serum albumin with other molecules like haeme or bilirubin (165). Effects on enzymes have also been demonstrated with other platinum compounds. Thus, platinum(IV) chloride has been found to affect drug metabolism and to inhibit DNA synthesis in rat (see Section 10.7. Other Studies).

Platinum compounds may also be reactive towards DNA (73). The chemical reactivity of the complexes differ very much and is dependent on the ligands (28). The interaction of the antineoplastic drug cisplatin with DNA has been extensively studied. Aspects of the molecular mechanism involve passive diffusion of the neutral complex across the cell membrane followed by hydrolysis and subsequent binding of the aquated platinum complex to DNA (24, 176). Some of the neutral platinum complexes, like cisplatin, are strong mutagens, and there seems to be a common pattern between mutagenic potency and antitumor activity in the cis-PtN_2X_2-type complexes (166). The mechanism of the mutagenic activity for compounds like cisplatin is believed to occur through the reaction with DNA by displacement of both chlorine atoms and subsequent chelate formation between N_7(G) and O^6(G) sites (166). DNA-binding experiments and metabolism studies in vivo and in vitro with some platinum(IV) complexes (iproplatin and tetraplatin), suggest

that this kind of complexes is reduced to divalent metabolites able to react with DNA (41, 122, 123). The interaction of complex or simple salts of platinum with DNA has not been very well investigated, 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 (26, 71, 72, 137, 151, 158, 159, 160, 161, 179).

10. Effects in animals and in vitro studies

10.1. Irritation and sensitisation

In a study on male albino rabbits (25) dermal irritancy (intact skin) and cellular toxicity (abraded skin) of platinum(IV) chloride, platinum(II) chloride and platinum(IV) oxide was tested. 0.1 g of the compound was mixed with 0.1 ml water and spread over an abraded or intact site, which was immediately covered. The skin reactions were evaluated and scored after 24 h and then 48 h later. Platinum(IV) chloride was judged as irritant on intact skin, whereas platinum(II) chloride and platinum(IV) oxide were considered as essentially nonirritant. Unpublished data (cited in 56, 63) on skin irritation (patch tests on rabbits; 24 h contact or 4 h contact) and eye irritation (rabbits) for some other platinum compounds are summarized in Table 10.

Irritation of the eyes and respiratory tract during exposure to ammonium hexachloroplatinate(IV) was reported in a russian study (133), but no details e.g. on exposure time, animal species or methods were given. 35 mg/m^3 was considered as a threshold concentration for an effect on the mucous membranes of the eyes.

An intense attack of asthma occurred in guinea-pigs, when the animals were exposed to an aerosol of sodium hexachloroplatinate(IV) (no dose given) or the compound was injected intravenously (10-20 mg/kg). Bronchospasm was also noted after a single intravenous injection of 1-2 mg/kg sodium hexachloroplatinate(IV), but after repeated doses of the chloroplatinate the response disappeared (120, 136). When sodium hexachloroplatinate(IV) was tested in rats it was shown to be less active than in guinea pigs, but pruritus of the muzzle and the feet, cooling of the extremities and increased histamine levels in plasma was demonstrated, when 40 mg/kg of the salt was injected intravenously. The intravenous injection of 30 mg/kg sodium hexachloroplatinate(IV) into an anaesthetized dog led to death after some minutes. The histamine content of the whole blood (expressed as dihydrochloride) increased considerably from 20 to 1000 μg/L in 2-5 minutes. No histamine release was found in another dog at the dose level 10 mg/kg (136).

Pulmonary hyperreactivity expressed as significantly increased average pulmonary flow resistance (R_L) and decreased forced expiratory volume ($FEV_{0.5}$/FVC) was found in male Cynomolgus monkeys challenged with sodium hexachloroplatinate(IV) aerosols (up to 62.5 mg/ml solutions) 2 weeks after a period of

Table 10. Skin and eye irritation by platinum compounds*

Compound	Score (skin)	Skin irritation test classification	Eye irritation test classification
Platinum (IV) oxide	0	non-irritant**	-
Platinum(II) chloride	0.2	non-irritant**	-
Platinum(IV) chloride	1.8	mild irritant**	-
Ammonium hexachloroplatinate(IV)	1.3	mild irritant	-
Ammonium tetrachloroplatinate(II)	2.7	slight irritant***	corrosive
Sodium hexachloroplatinate(IV)	0.5	mild irritant	irritant
Sodium hexahydroxyplatinate(IV)	5.4	severe irritant	-
Potassium tetrachloroplatinate(II)	0	non-irritant	irritant
Potassium tetracyanoplatinate(II)	0.3	mild irritant	irritant****
Tetraammineplatinum(II) chloride	2.8	moderate irritant	strongly irritant
Diamminedinitroplatinum(II)	0	non-irritant	severely irritant

*Unpublished data cited in 63. Tests on rabbits were carried out according to US Federal Register 1973 guidelines (skin and eye tests) or according to OECD Test Guideline no 404 (skin) or 405 (eye).
**25. The given primary irritation score refer to intact skin.
***It is stated in 56, that this compound produced pronounced skin irritation.
****It is stated in 56, that this compound would not be classified as irritant to the eye according to current EC classification criteria.

repeated inhalation exposure to about 216 μg/m^3 of the platinum salt (4h/day, biweekly for 12 weeks; particle size (MMAD) 1.61 μm), while no signs of bronchial hyperreactivity (compared to control group mean responses) was found at an exposure level around 1940 μg/m^3 (MMAD 1.27 μm) or after percutaneous exposure (1 ml of a solution of 20 mg/ml Na_2PtCl_6 biweekly for 12 weeks). However, marked effects on the pulmonary function was found in all exposed and control animals challenged with the platinum salt (controls: significant impairments after challenge with the highest concentration of Na_2PtCl_6), and these results indicate a pharmacologic or irritant-mediated bronchoconstriction mechanism for acute exposure to this compound. No effect on post-exposure baseline pulmonary function (saline challenge) was found with the exposure regimens used in this study and no differences in dermal sensitivities to sodium hexachloroplatinate(IV) was observed in any of the groups. When compared on the basis of monkey to human minute volume ratio a concentration of 200 μg/m^3 (4 h/day biweekly for 12 weeks), according to the authors, result in an equivalent exposure of 3 to 4 times of that to which a worker would be exposed in 1 week at the air level 2 μg/m^3 (17).

In further experiments in male Cynomolgus monkeys, combined inhalation exposure of 200 μg/m^3 ammonium hexachloroplatinate(IV) (MMAD 1.07 μm) and 1 ppm ozone 6 h/day, 5 days per week for 12 weeks was shown to significantly reduce (difference in postexposure and preexposure values) the concentration of platinum salt (sodium hexachloroplatinate(IV)) and methacholine necessary to increase average pulmonary flow resistance (R_L) by 200%, indicating that combined exposure increased both specific and nonspecific bronchial hyperreactivity more often than did exposure to either ozone or the Pt salt alone. Some animals with

combined exposure exhibited extremely elevated R_L values and haemoptysis (expectoration of blood) after challenge with the most dilute solutions. Combined exposure also significantly increased the incidence of positive skin tests to platinum (intracutaneous test) when compared with exposure to platinum or ozone alone. The baseline pulmonary function (saline challenge) was not significantly affected by the exposure regimens and exposure to ammonium hexachloroplatinate(IV) or ozone alone (mean values) had no significant effects on postexposure Pt or methacholine reactivity (16).

In a study in female Hooded Lister rats (103) conjugation of ammonium tetrachloroplatinate(II) with ovalbumin produced conjugates (administered with adjuvant) capable of inducing IgE antibody (PCA challenge, RAST), whereas no specific IgE antibody was induced in animals given free platinum salt (1 μg-1 mg via various routes including intratracheal). Significant cross reactivity (PCA-tests) in Hooded Lister rats immunized with ovalbumin-ammonium tetrachloroplatinate, between ammonium tetrachloroplatinate(II), ammonium hexachloroplatinate(IV) and the conjugated tetrachloroplatinate was found by the same authors, while there was no cross-reactivity with the compounds cesium trichloronitroplatinate(II), cisplatin, potassium tetracyanoplatinate(II) and tetraammineplatinum(II) chloride (104). In a later study (105) repeated injections of ammonium tetrachloroplatinate(II) (100 μg/kg bw three times a week for 3 weeks; adjuvant) to female Hooded Lister rats immunised with antigen (OVA) was shown to give elevated levels of total IgE as well as raised RAST levels (specific IgE antibody directed against ovalbumin).

In a study for US EPA (157) the potential for platinum(IV) sulphate and platinum(IV) chloride to elicit skin sensitisation was investigated in a number of laboratory animals. No allergic induction was shown, when platinum(IV) sulphate was repeatedly injected (0.05-0.35 mg/ml subcutaneously or intravenously) into albino rabbits, albino guinea pigs and white Swiss mice or platinum(IV) sulphate paste was repeatedly applied to rabbits and guinea pigs (0.1-0.25 g/application). The animals were tested by intradermal skin test (rabbits, guinea pigs) and footpad test (mice). When guinea pigs were skin tested 14 days after the last subcutaneous injection of platinum(IV) chloride (1.5-4.5 mg/ml) the skin test reactions were also found to be negative. Furthermore, platinum-albumin complexes injected subcutaneously at various concentrations (and later skin tested intradermally) failed to induce an allergic response to platinum in rabbits and guinea pigs (157). However, no positive control substances were used to demonstrate the effectiveness of the test procedures.

Immunogenicity of Pt salts was demonstrated in mice by means of the popliteal lymph node (PLN) assay. There were differences in the degree of response between the various strains used on the study (BALB/c, DBA/2, C57BL/6, B10.S, C3H/He, NMRI +/nu, NMRI, NMRI nu/nu) and it was shown that mice deficient of T-lymphocytes completely failed to respond. A single subcutaneous injection of dissolved hexachloroplatinates ($Na_2(PtCl_6)$, $(NH_4)_2(PtCl_6)$) without adjuvant induced a dose-dependent lymph node activation (determined by an increase in both PLN weight and cellularity) in mice of strain C57BL/6. Significant PLN reactions were induced at doses about 20-160 μg/animal (45-360 nmol/animal; about 1-8

mg/kg bw) and peak reactions were obtained around day 6 after administration of about 40-80 μg/animal (90-180 nmol per animal; about 2-4 mg/kg bw). Mice sensitised to $(PtCl_6)^{2-}$ mounted an enhanced response upon local restimulation with suboptimal doses of the same, but not unrelated compounds, indicating a specific secondary response (about one fifth of the primary dose proved to be sufficient for elicitation of a secondary response with $Na_2(PtCl_6)$ = 36 nmol/animal; 16 μg/animal; about 0.8 mg/kg bw) (143). Apart from hexachloroplatinates, equimolar amounts of sodium tetrachloroplatinate(II) elicited a strong primary PLN response. Lower but still significant PLN indices were obtained with cisplatin, which had to be tested at a lower dosage due to its limited solubility (strains C57BL/6 or BALB/c were used for the various Pt compounds) (143). In a modified test system in C57BL/6 mice 3x2 μg sodium hexachloroplatinate(IV)/mouse was injected weekly (sc or ip) for 20 weeks or 0.2 μg sodium hexachloroplatinate(IV)/mouse/week was dripped in the nose for 20 weeks and spleen cells from treated animals were then injected subcutaneously (up to 22 weeks after cessation of treatment) into untreated animals. 24 hours later a suboptimal dose of the compound (18 nmol; 8 μg/animal; about 0.4 mg/kg bw) was injected (untreated mice) and it was shown that a PLN reaction was elicited and that the nasal route of administration had been the most efficient in inducing immunity (144, 145). Unpublished results (cited in 144) concerning platinum(IV) chloride, platinum(II) chloride, platinum(IV) oxide and platinum metal showed that the soluble Pt compound caused PLN reactions, but as platinum(IV) chloride is not very stable in solution it was considered that the reactions was caused by formed complexes. The insoluble Pt compounds could not be evaluated in this test.

Ammonium tetrachloroplatinate(II) has been tested in the guinea-pig maximization test (GPMT) in albino Dunkin-Hartley guinea-pigs and a local lymph node assay (LLNA) in CBA/Ca mice to predict the skin sensitisation potential. The compound was classified as an extreme sensitiser in GPMT (intradermal induction injections 0.05%; induction patch 5%, challenge patch 1%) and found to be positive (gave a proliferative response) in LLNA (the test substance was assayed at three concentrations; topical application of 2.5, 5 or 10%) (9).

10.2. Effects of single exposure

The acute toxicity of platinum depends on the compound, the dose and the route of administration. Generally the toxicity of platinum compounds is much higher by intraperitoneal or intravenous administration than by oral administration. There are insufficient data, however, concerning inhalation exposure (50, 63). Within a given class of Pt compounds the acute toxicity follows the water solubility to some degree and thus, water soluble compounds usually are more toxic than insoluble ones (49, 50, 63, 108). Some LD_{50} values for rats are tabulated in Table 11. In a study in rat, the pretreatment with a lower dose of platinum(IV) chloride, 48 hours before a higher generally lethal dose (113 μmol/kg) of the compound, markedly increased the survival (51).

Platinum metal appears to have low acute toxicity at oral administration, but the highly dispersed powder, although insoluble in water, might be absorbed to some extent from the gastrointestinal tract. When orally administered to rats as fine dust (1-5 μm; doses not specified) necrotic changes in the gastrointestinal epithelium, granular dystrophy of hepatocytes, and signs of swelling in the epithelium of the convoluted renal tubules was observed in a poorly reported russian study (133). The highest dose given (25167 μg/kg according to personal communication to IPCS) was not lethal.

Few details on the clinical signs of acute toxicity of platinum salts are given in the literature. However, in an unpublished report (Degussa, 1989a, cited in 63) signs of poisoning with ammonium tetrachloroplatinate(II) are described and include diarrhoea, clonic convulsions, laboured respiration and cyanosis. Hexachloroplatinic(IV) acid was shown in one study (171) to be highly nephrotoxic in male F344 (Fischer CDF) rats. Rats died of renal failure, hypocalcemia, and hyperkalemia after a singel intraperitoneal injection of 40-50 mg/kg. The tubular necrotizing lesions involved the entire renal cortex. Severe histopathological lesions were also observed in thymus (171). When platinum(IV) sulphate was administered intragastrically as a single dose, at the LD_{25} level (213 mg Pt/kg), to mice general activity expressed as open field behaviour (ambulations) was significally depressed, while exploratory behaviour was not affected (85).

Table 11. Some LD_{50} values* after peroral (po) or intraperitoneal (ip) administration of platinum compounds to rats

Compound	Route	LD_{50} (mg/kg)	LD_{50} (mg Pt/kg)
Platinum (IV) oxide	po	>8000[c], >3405[a]	>6900[c], >2926[a]
Platinum(II) chloride	po	>2000[c], >1330[a]	>1400[c], >975[a]
Platinum(II) chloride	ip	670[c]	490[c]
Platinum(IV) chloride	po	240[c]	136[c]
Platinum(IV) chloride	ip	38[c]	22[c]
Platinum(IV) sulphate ($4H_2O$)	po	1010[a]	430[a]
Platinum(IV) sulphate ($4H_2O$)	ip	138[c]-184[c], 310[c]-312[a]	59[c]-78[c], 132[c]-133[a]
Hexachloroplatinic(IV) acid	ip	40[b]-50[b]	15[**b]-19[**b]
Ammonium tetrachloroplatinate(II)	po	125-212	65-111
Ammonium hexachloroplatinate(IV)	po	200	88
Potassium tetrachloroplatinate(II)	po	50-200	23-94
Potassium tetracyanoplatinate(II)	po	>2000	>1770
Sodium hexachloroplatinate(IV)	po	25-50	11-21
Sodium hexahydroxyplatinate(IV)	po	500-2000	284-1137
Tetraammineplatinum(II) chloride	po	>15000	>8759
Diamminedinitroplatinum(II)	po	5000, >5110	3037, >3104

*The LD_{50} values are taken from unpublished reports cited in 63 unless otherwise is stated. Other references used are [a]50, [b]171 and [c]49. If the LD_{50} value is expressed as mg/kg as well as mg Pt/kg in the reference both values are used in the table, otherwise the mg Pt/kg-values have been calculated from the given LD_{50} values.
**Counted as the hexahydrate.

10.3. 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.

A reduction in weight gain by about 20%, probably related to a decrease in feed and fluid consumption, was observed in male Sprague-Dawley rat during the first week when 550 mg/L (1.63 mmol/L) of platinum(IV) chloride was added to the drinking-water for 4 weeks (total intake of approximately 250 mg Pt/rat or about 43 mg Pt/kg bw/day). A concentration of about 180 mg/L (0.54 mmol/L; total intake 60 mg Pt/rat or about 10 mg Pt/kg bw/day) for 4 weeks did not affect the normal weight gain (50). An increase in kidney weight by about 6-10% ($p<0.05$) was also noted at the higher dose level, when the compound was administered for 4 weeks, while the weights of the five organs investigated (liver, kidney, spleen, heart, testes) were not affected when the same dose was given for 8 days or at a concentration of 180 mg/L (0.54 mmol/L) for 29-30 days (total intake approximately 60 mg Pt/rat in the two latter experiments; about 60 and 10 mg Pt/kg bw/day) (50). When platinum(IV) sulphate (tetrahydrate) was administered at a concentration of about 750 mg/L (1.63 mmol/L; totally approximately 60 mg Pt/rat or 59 mg Pt/kg bw/day) in the drinking fluid for about 1 week the weight gain was reduced, while the organ weights were not significantly affected (50). In studies with other platinum compounds (49, 51, 100) it was shown, that platinum(IV) oxide had no effect in male Sprague-Dawley rats on weight gain during each of 4 weeks, when present in the feed at a level of 6.8 g/kg (29.8 mmol/kg diet; total dose 4.9 g Pt/rat, corresponding to about 700 mg Pt/kg bw/day), while there was a decrease in weight gain (and water consumption) in albino rats (Charles River CD-1-strain) given drinking water containing 235 mg/L (ppm) or 470 mg/L (ppm) potassium tetrachloroplatinate(II) for 23 days.

No influence on body weight gain or food consumption was noticed in a study in male Sprague-Dawley rats, when platinum was added in the diet in the form of platinum(II) chloride or platinum(IV) chloride in amounts of up to 50 mg Pt/kg diet for 4 weeks (total average intake of platinum up to 21 mg/rat or on average 5 mg Pt/kg bw/day). In the case of platinum(IV) chloride there was a tendency towards decrease in the counts of erythrocytes as well as haematocrit with increasing amounts of the compound (at the highest dose level about 13%), whereas the volume of erythrocytes as well as haemoglobin content were not influenced. A significant increase of creatinine content in plasma also was shown at the highest dose level (platinum(IV) chloride) (130). When female Sprague-Dawley rats were fed a diet containing either platinum(IV) chloride or platinum metal in a concentration of 0.1, 0.5, 1.0, 50 and 100 mg Pt/kg diet (ppm) respectively, four weeks before pregnancy to twentieth day of gestation, there were no changes in haematological values (haemoglobin content, haematocrit, count and volume of erythrocytes) after intake of platinum(IV) chloride, while intake of platinum metal at the 100 ppm level (totally 88 mg Pt/rat or around 7 mg Pt/kg bw/day) led to a significant increase in red blood cell count. Growth rate and organ weights (liver, kidney

and spleen) of the mothers were uninfluenced of the intake of platinum(IV) chloride or platinum metal (18, 19). In two other studies (5, 6) no clinical signs of toxicity and no effect on feed intake, growth, haemoglobin content of blood, haematocrit or count and volume of erythrocytes was observed in male Sprague-Dawley rats after administration of up to 50 mg/kg (ppm) platinum metal powder in the diet for 4 -12 weeks (particle size 0.5-150 μm; 6).

No overt 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) or 208 $\mu g/m^3$ ammonium hexachloroplatinate(IV) and 1 ppm ozone for 12 weeks (6 h/day, 5 days per week; MMAD 1 μm) (16). However, the study was designed to detect differences in immunologic parameters and effects in the airways.

Chronic intoxication in rats after inhalation of 18.6 mg/m^3 ammonium chloroplatinate (no exposure time is given) was reported in a Russian study (133) and included reduction in body mass, decrease in the content of haemoglobin in blood, decrease in cholinesterase in blood, increase in acid phosphatase, alkaline phosphatase, alanine aminotransferase and aldolase, disturbances in carbohydrate and lipid metabolism, reduced concentrating capacity of the kidney, increased concentration of urea in blood and morphological changes reminiscent of glomerulonephritis. At the exposure level 4.5 mg/m^3 the effects were reported to be poorly expressed and reversible (disappeared after 30 days of recovery). However, the study is only described in brief and there are shortcomings (e.g. no values for exposed versus unexposed animals are presented and the contribution of platinum versus palladium to the toxic effects are difficult to interpret) and thus the reliability of the results are unclear.

10.4. Mutagenicity and genotoxicity

The antineoplastic agent cisplatin (cis-dichlorodiammineplatinum(II)) has been shown to bind to DNA and to be mutagenic in vitro and in vivo (61, 62, 74, 102, 155). Mutagenic activity has been found in vitro with other Pt compounds too, especially complexes with the same square-planar configuration of cis-PtN_2X_2 as cisplatin (166). Cytotoxicity is a common property of many Pt(II) and Pt(IV) complexes and some novel ammine/amine platinum(IV) dicarboxylates have been found to be at least 100 times more cytotoxic than cisplatin in vitro (74, 132). At least part of the increased cytotoxicity of the dicarboxylates over cisplatin may be attributable to an increased intracellular accumulation due to enhanced lipophilicity (74).

10.4.1. Effects in bacteria

The influence of molecular structure on mutagenicity was examined in a study (166) using Salmonella typhimurium TA 98 and TA 100. Seven of the 15 platinum compounds tested (0.8-100 nmol/plate) were considered direct mutagens as their mutagenicity was not dependent on metabolic activation by S9 mix. Strong mutagenicity and high toxicity for both bacterial strains were exhibited by cisplatin and three

other compounds with a molecular structure similar to cisplatin (cis-PtN_2X_2), whereas relatively strong mutagenicity (toxicity was also observed) was noticed with the complex salt chlorotriammineplatinum(II) tetrachloroplatinate(II) (Cleve´s salt). The charged compounds potassium tetrachloroplatinate(II) and hexachloroplatinic(IV) acid (hexahydrate) showed weak mutagenicity, the latter only after metabolic activation (TA 98). Cis-potassium dichlorodinitroplatinate(II) also showed weak mutagenic activity, but only without metabolic activation (TA 98). Potassium hexakis(thiocyanato) platinate(IV) and potassium hexabromoplatinate(IV) showed toxicity in both strains but mutagenicity was not observed due to killing. Among the compounds not showing mutagenic activity were: tetraammineplatinum(II) chloride, cis-dinitrodiammineplatinum(II), potassium tetranitroplatinate(II) dihydrate and barium cyanideplatinum(II) tetrahydrate (166).

Similarly, it was found in earlier studies in Salmonella typhimurium TA 100, that the charged platinum compounds (e.g. potassium tetrachloroplatinate(II), potassium amminetrichloroplatinate(II), tetraammineplatinum(II) chloride, chlorotriammineplatinum(II) chloride) generally had low mutagenicity, whereas neutral compounds with a cis-PtN_2X_2 structure had definite mutagenic properties (79, 80). Cisplatin was the by far most mutagenic of the compounds tested (79, 80). However, an obvious mutagenic activity of potassium amminetrichloroplatinate(II) and ammonium amminetrichloroplatinate(II) was found in one study (121) on different strains of Salmonella typhimurium (TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537, TA 1538) and in an unpublished study (cited in 56) tetraammineplatinum(II)chloride was found to be mutagenic in Salmonella strain TA 1537 (tested in TA 98, TA 100, TA 1535, TA 1537, TA 1538). When different platinumchloroammine complexes were investigated in a study in Salmonella typhimurium in order to find a correlation between chemical reactivity and biological activity it was found, that a structure of a neutral complex creating a very labile ligand gave more toxic but less mutagenic complexes than cisplatin (28).

In a study using five strains of Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and two strains of Escherichia coli (B/r WP2 try, WP2 hcr try) ammonium hexachloroplatinate(IV) and platinum(IV) chloride were stated to be potent mutagens. Ammonium hexachloroplatinate(IV) was found to induce mutations in one strain of E. coli and in Salmonella typhimurium TA 98, whereas platinum(IV) chloride was mutagenic only in Salmonella typhimurium TA 98 (concentrations not given). Hexachloroplatinic(IV) acid was not positive in these assays. The same authors showed that hexachloroplatinic(IV) acid (0.01 mol/L), ammonium hexachloroplatinate(IV) (0.1 mol/L) and platinum(IV) chloride (0.001 mol/L) were strongly genotoxic in the Bacillus subtilis rec-assay (71).

Table 12. Genetic activity of some platinum compounds in short-term tests in vitro

Compound	Indicator cell	With or without S9	Doses tested	Genetic activity	Ref
Platinum(II) chloride	mouse lymph. cell line L5178Y	-	0-800 µmol/L	-	137
Platinum(IV) chloride	S. typhimur. TA 98	-	not given	+	71
	S. typhimur. TA 100	-	not given	-	71
	S. typhimur. TA 1535	-	not given	-	71
	S. typhimur. TA 1537	-	not given	-	71
	S. typhimur. TA 1538	-	not given	-	71
	E. coli B/r WP2 try	-	not given	-	71
	E. coli WP2 hcr try	-	not given	-	71
	B. subtilis H17, M45	-	0.001 mol/L	+	71
	Saccharom. F 51	-	0-0.3 mmol/L	+	48
	V79 cells	-	0-15 µmol/L	+	72
	CHO-S cells	-	0-70 µmolL	+	159
	CHO-AUXB1 cells	-	0-25 µmol/L	+	159
	SHE cells	-	0-0.12 µmol/L	+	26
	mouse lymph. cell line L5178Y	-	25-150 µmol/L*	+	137
Platinum(IV) sulphate	CHO-S cells	-	0-160 µmol/L	+	158
	CHO-S cells	-	up to 550 µmol/L	+	151
	CHO-AUXB1 cells	-	0-150 µmol/L	+	161
Hexachloro-platinic(IV) acid	S. typhimur. TA 98	-	not given	-	71
	S. typhimur. TA 98	+	0.8-100 nmol/plate	+	166
	S. typhimur. TA 98	-	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	not given	-	71
	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
	S. typhimur. TA 1535	-	not given	-	71
	S. typhimur. TA 1537	-	not given	-	71
	S. typhimur. TA 1538	-	not given	-	71
	E. coli B/r WP2 try	-	not given	-	71
	E. coli WP2 hcr try	-	not given	-	71
	B. subtilis H17, M45	-	0.01 mol/L	+	71
Ammonium hexachloro-platinate(IV)	S. typhimur. TA 98	-	not given	+	71
	S. typhimur. TA 100	-	not given	not concl.	71
	S. typhimur. TA 1535	-	not given	not concl.	71
	S. typhimur. TA 1537	-	not given	-	71
	S. typhimur. TA 1538	-	not given	-	71
	E. coli B/r WP2 try	-	not given	-	71
	E. coli WP2 hcr try	-	not given	+	71
	B. subtilis H17, M45	-	0.1 mol/L	+	71

Table 12. Cont.

Compound	Indicator cell	With or without S9	Doses tested	Genetic activity	Ref
Potassium tetra-	S. typhimur. TA 98	+	0.8-100 nmol/plate	+	166
chloroplatinate(II)	S. typhimur. TA 98	-	0.8-100 nmol/plate	+	166
	S. typhimur. TA 100	+	0.8-100 nmol/plate	+	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	+	166
	S. typhimur. TA 100	not given	150 μg/plate**	+	79
	Saccharom. cerevisiae	-	42 μg/ml***	+	153
	CHO-S cells	-	40 μmol/L****	-	158
	CHO-AUXB1 cells	-	0-103 μmol/L	+	160
	CHO-K_1-BH_4 cells	-	0-65 μmol/L	+/-	57,68
Potassium hexa-	CHO-S cells	-	up to 220 μmol/L	+	151
chloroplatinate(IV)	CHO-S cells	-	10 μmol/L 60 μmol/L****	+	158
	CHO-AUXB1 cells	-	0-103 μmol/L	+	160
cis-Potassium	S. typhimur. TA 98	+	0.8-100 nmol/plate	-	166
dichlorodinitro-	S. typhimur. TA 98	-	0.8-100 nmol/plate	+	166
platinate(II)	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
Potassium tetra-	S. typhimur. TA 98	+	0.8-100 nmol/plate	-	166
nitroplatinate(II)	S. typhimur. TA 98	-	0.8-100 nmol/plate	-	166
dihydrate	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
Barium cyanide-	S. typhimur. TA 98	+	0.8-100 nmol/plate	-	166
platinum(II) tetra-	S. typhimur. TA 98	-	0.8-100 nmol/plate	-	166
hydrate	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
Ammonium	S. typhimur. TA 92	-	12.5-50 μg/well	+	121
amminetrichloro-	S. typhimur. TA 94	-	12.5-50 μg/well	+	121
platinate(II)	S. typhimur. TA 98	-	12.5-50 μg/well	+	121
	S. typhimur. TA 100	-	12.5-50 μg/well	+	121
	S. typhimur. TA 1535	-	12.5-50 μg/well	+	121
	S. typhimur. TA 1537	-	12.5-50 μg/well	+	121
	S. typhimur. TA 1538	-	12.5-50 μg/well	-	121
Potassium	S. typhimur. TA 92	-	25-100 μg/well	+	121
amminetrichloro-	S. typhimur. TA 94	-	25-100 μg/well	+	121
platinate(II)	S. typhimur. TA 98	-	25-100 μg/well	+	121
	S. typhimur. TA 100	-	25-100 μg/well	+	121
	S. typhimur. TA 100	not given	10 μg/plate**	+	79
	S. typhimur. TA 1535	-	25-100 μg/well	+	121
	S. typhimur. TA 1537	-	25-100 μg/well	+	121
	S. typhimur. TA 1538	-	25-100 μg/well	+	121
	CHO-K_1- BH_4 cells	-	0-50 μmol/L	+	57,68

Table 12. Cont.

Compound	Indicator cell	With or without S9	Doses tested	Genetic activity	Ref
Chlorotriammine platinum(II) tetrachloroplatinate(II) (Cleve´s salt)	S. typhimur. TA 98	+	0.8-100 μmol/plate	+	166
	S. typhimur. TA 98	-	0.8-100 μmol/plate	+	166
	S. typhimur. TA 100	+	0.8-100 μmol/plate	+	166
	S. typhimur. TA 100	-	0.8-100 μmol/plate	+	166
Chlorotriammine platinum(II) chloride	S. typhimur. TA 100	not given	50 μg/plate**	+	79
	CHO-K_1- BH_4 cells	-	0-360 μmol/L	+	57,68
Tetraammine-platinum(II) chloride	S. typhimur. TA 98	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 98	-	0.8-100 nmol/plate	-	166
	S. typhimur. TA 98	not given	not given	-	56
	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	not given	not given	-	56
	S. typhimur. TA 100	not given	>250 μg/plate**	+	79
	S. typhimur. TA 1535	not given	not given	-	56
	S. typhimur. TA 1537	+	not given	+	56
	S. typhimur. TA 1537	-	not given	+	56
	S. typhimur. TA 1538	not given	not given	-	56
	CHO-K_1- BH_4 cells	-	0-6600 μmol/L	-	57,68
cis-Dinitro-diammine-platinum(II)	S. typhimur. TA 98	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 98	-	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	+	0.8-100 nmol/plate	-	166
	S. typhimur. TA 100	-	0.8-100 nmol/plate	-	166
Dinitrodiammine-platinum(II)	mouse lymph. cell line L5178Y	-	0-200 μmol/L	-	137

*the doses are not clearly given
**maximal dose in the reversion test within the linear dose-response curve (all doses not given)
***maximal efficient dose (all doses not given)
****all doses not given
+/- marginal

10.4.2. Effects in yeast

In a study on growing yeast cells (Saccharomyces strain F51 and 2200) platinum(IV) chloride as well as cisplatin was found to strongly inhibit DNA, RNA and ribosome synthesis. A comparison of the concentrations required to produce a 50% inhibition showed that platinum(IV) chloride was more efficient in inhibiting DNA synthesis than cisplatin (I_{50} 0.2 mmol/L versus 0.42 mmol/L), while cisplatin was more efficient in inhibiting cell growth (I_{50} 0.6 mmol/L versus 1.1 mmol/L) (48).

In a system to detect chromosome number abnormalities occurring during meiosis in Saccharomyces cerevisiae a weak induction of diploid spores was found with potassium tetrachloroplatinate(II) (maximal efficient dose 42 μg/ml) (153).

10.4.3. Effects in mammalian cells

Six square-planar platinum(II)chloroammines with the charge ranging from +2 {$[Pt(NH_3)_4]^{+2}$} to -2 {$[PtCl_4]^{-2}$} and the number of reactive sites varying from 4 (tetrachloride) to 0 (tetraammine) was tested in a structure-mutagenicity study with the CHO/HGPRT (hypoxanthine-guanine phosphoribosyl transferase)-system. Three of the compounds exhibited mutagenic activity and among them cisplatin was the most potent. Based on the slope of the linear portion of the mutation induction curve, the approximate relative mutagenic activity of cisplatin, potassium trichlor-ammineplatinate(II) and chlorotriammine platinum(II) chloride was 100:8:0.3. The mutation frequency of potassium tetrachloroplatinate(II) was less clear, but judged to be marginal, whereas no mutagenicity was found with tetraammineplatinum(II) chloride. The relative cytotoxicity of the compounds followed the same order as the mutagenicity (57, 68).

A dose-dependent increase in mutant frequency was found with cisplatin, platinum(IV) sulphate and platinum(IV) chloride in CHO-S cells using 8-azaguanine (8-AG) for mutant selection, following a 20 h exposure (158, 159). Cisplatin was calculated by the authors to be 38-fold more mutagenic than platinum(IV) sulphate. Identical 20 h exposures to varying amounts of e.g. potassium tetrachloro-platinate(II) and potassium hexachloroplatinate(IV) did not induce 8-AG mutants. However, an increased exposure period (10-25 population doublings) potassium hexachloroplatinate(IV) (10 μM) was weakly mutagenic (158). None of the compounds were as effective as cisplatin at inhibiting cell growth (I_{50}=0.9 μM).

In studies on CHO AUXB1 cells (159, 160, 161) a dose-dependent increase above the spontaneous revertant frequency (at concentrations where the cell survival remains high), reflecting mutations involving the FPGS (folylpolyglutamate synthetase) gene locus, was induced after 20-22 h exposure with cisplatin, platinum(IV) sulphate, platinum(IV) chloride, potassium tetrachloroplatinate(II) and potassium hexachloroplatinate(IV). Platinum(IV) sulphate was about 50 times less mutagenic than cisplatin on a concentration basis (161).

Cellular resistance to the toxic effects of potassium hexachloroplatinate(IV) (220 μM) and platinum(IV) sulphate (550 μM) (quantitated by comparing plating efficiencies), interpreted by the authors to be a result of mutation and selection, was induced separately in cultured CHO-S cells by continuous exposure to the compounds for 5 and 4 months, respectively (151).

Induction of mutation by platinum(IV) chloride was measured utilizing the HGPRT locus in V79 cells. Treatment with 15 μM of platinum(IV) chloride increased the mutation frequency at rates of around 7 times control rates (72).

In a mutagenic test with mouse lymphoma cells line L5178Y cisplatin and platinum(IV) chloride, but not platinum(II) chloride and dinitrodiammineplatinum(II), were found to be mutagenic at the thymidine kinase locus. Cisplatin was more potent as a mutagen than platinum(IV) chloride (137).

Platinum(IV) chloride (0.03-0.12 mM) was found to significantly enhance viral transfomation of Syrian hamster embryo cells (26).

10.4.4. Effects in vivo

A significant increase in recessive sex-linked lethal mutations was found after feeding of $1.5x10^{-3}$M platinum(IV) chloride solution for 48 hours or $3x10^{-4}$M platinum(IV) chloride solution for 72 hours to adult males of fruitfly (Drosophila melanogaster) (179). In two other studies (unpublished reports, cited in 56) tetraammineplatinum(II) chloride and potassium tetrachloroplatinate(II) did not induce any increase in the frequency of sex-linked recessive lethal mutations in male fruitfly up to doses which produced about 50% lethality, but without causing sterility.

In micronucleus studies (unpublished reports, cited in 56) tetraammine-platinum(II) chloride and potassium tetrachloroplatinate(II) were administered as a single oral dose to male and female mice and bone marrow was sampled 24 hours later. No effect was seen in the numbers of micronucleated polychromatic erythrocytes (PCE) or on (PCE)/normochromatic erythrocytes ratio. However, the highest doses used (5000 mg/kg: $Pt(NH_3)_4Cl_2$; 150 mg/kg: K_2PtCl_4) resulted in deaths. The clastogenic effects of these two compounds were also investigated in male and female Chinese hamsters, which received oral gavage doses daily for 5 days. No effect was observed on the frequency of aberrant metaphases following treatment with either substance. Tetraammineplatinum(II) chloride produced a dose-related decrease in body weight and one animal in the highest dose group (1000 mg/kg) died; there was also some indication of a reduction in the mitotic index of bone marrow cells in a preliminary study, which included main-test doses. For potassium tetrachloroplatinate(II) there was a general reduction in the mitotic index (2.9-3.1%) in the treated animals compared to controls (4.6%) (unpublished reports, cited in 56). Overall it was concluded, that tetraammineplatinum(II) chloride and potassium tetrachloroplatinate(II) did not induce any mutagenic effects in the bone marrow cells of mouse or hamster.

It can be concluded, that most of the described complexes/salts of platinum are genotoxic/mutagenic in vitro (Table 12), but there generally is a lack of information from in vivo studies.

10.5. Carcinogenic effects

No relevant studies on the carcinogenicity of platinum and platinum compounds, except for cisplatin and certain related compounds, have been found. Cisplatin has been shown to cause extensive DNA damage at low doses and there is sufficient evidence for carcinogencity of cisplatin (cis-dichlorodiammineplatinum(II)) in animals (61, 62). Some other antitumor cis-platinum(II) coordination complexes shown to be carcinogenic in rodents are cis-dichlorobis(cyclopentylamine)-platinum(II) and cis-dichlorobis(pyrrolidine)-platinum(II) (80).

10.6. Reproductive and developmental effects

Influences of alimentary platinum(IV) chloride and platinum metal on reproduction were studied in female Sprague-Dawley rats (18). The animals were fed a diet con-

taining 0.1, 0.5, 1.0, 50 and 100 mg Pt/kg diet (ppm) either of platinum(IV) chloride or platinum metal for four weeks before pregnancy to twentieth day of gestation. Neither the average wet weight of foetus and placenta nor the average number of normal and absorbed foetus were dependent on the Pt-ingestion of the mothers. Thus, no increase in external malformations were seen. When platinum(IV) chloride or platinum(II) chloride was given in concentrations up to 100 mg Pt/kg in the diet to lactating rats (21 days) no influence on the weight of the offspring or on count and volume of erythrocytes, haematocrit and haemoglobin in maternal blood/blood of offspring was found (77).

Effects on the development of offspring were investigated in female Swiss ICR mice exposed to platinum(IV) sulphate or sodium hexachloroplatinate(IV) during pregnancy or lactation (30). A single intragastric dose of platinum(IV) sulphate (200 mg Pt/kg) or a single subcutaneous dose of sodium hexachloroplatinate(IV) hexahydrate (20 mg Pt/kg) at the LD_1 level was administered on day 7 or 12 of gestation or on day 2 post-partum. The pups were cross-fostered to treated or untreated dams at birth. Rate of growth and gross activity of the neonates were assessed. On day 60-65 postpartum open-field behavior (ambulation and rearing), rotarod performance, and passive avoidance learningwere investigated in the adult offspring. The predominant effect of maternal administration of platinum(IV) sulphate on day 7 and 12 of gestation was reduced offspring weight. This effect continued through day 45 postpartum. Type of foster-mother exposure also had a significant effect on offspring weight. For example on day 45 postpartum, no matter what their gestational history, pups reared by foster mothers exposed to platinum during gestation weighed less than pups reared by control mothers. In the platinum(IV) sulphate lactational study (treatment on day 2 postpartum), pups reared by mothers receiving platinum(IV) sulphate were less active than pups reared by control mothers. The effects on neonatal and adult offspring of maternally administered sodium hexachloroplatinate(IV) were limited to exposure on day 12 of gestation and were expressed in some of the tests as a reduced activity level.

Platinum(IV) chloride, injected by the intratesticular route in albino rats (single dose; 0.08 mmole/kg bw or 27 mg/kg bw) or by the subcutaneous route in Swiss mice (30 days; total dose 0.08 mmole/kg bw or 27 mg/kg bw), was shown to cause a large reduction in testis weight. Total testicular necrosis and destruction of all spermatozoa was seen within two days in rat, while spermatogenic arrest at the primary spermatocyte or spermatogonial stages (without affecting the interstitium) was found in mouse (70). When strips of platinum metal was tested in vitro (incubation time 2-5 h) a weak inhibition of human sperm motility was found in one study (75). In a later study (52) no significant reduction in motility of human spermatozoa was shown (platinum metal; in vitro), but if the incubation had been prolonged beyond three hours, a small spermicidal effect may have been observed in this study.

10.7. Other studies

The local action of the sodium hexachloroplatinate(IV) has been studied in guinea-pig. The injection of 0.2 ml of a 10^{-4} g/ml solution into the abdominal skin was fol-

lowed by an increased capillary permeability, demonstrated by showing the local accumulation of Evans Blue (136). When skin testing (Evans blue dye iv and after 15 minutes serial dilutions of $1x10^{-7}$ to $1x10^{-3}$ g/ml solutions of Na_2PtCl_6 intradermally) was performed on male Cynomolgus monkeys before and after 12-week exposure regimens (biweekly) with sodium hexachloroplatinate(IV) (200 $\mu g/m^3$, 2000 $\mu g/m^3$ or 1 ml of 20 mg/ml Na_2PtCl_6 percutaneously) positive dermal bluing reactions were obtained with 12 of 19 animals at dilutions of 10^{-5} g/ml. However, the results showed no change in the extent of dye leakage before and after the exposure (17).

Enzymes regulating the haeme pathway in liver and kidney was affected in male Sprague-Dawley rats, when potassium hexachloroplatinate(IV) or potassium tetrachloroplatinate (II) was given subcutaneously as a single dose of 60 mg/kg (125 μmol/kg bw) and 52 mg/kg (125 μmol/kg bw), respectively (86, 117). Interaction with the degradation of haeme via the enzyme haeme oxygenase (transient depression followed by stimulation) was noticed in one study (86) and it was shown, that microsomal haeme and cytochrome P450 contents had diminished substantially in liver and kidney when the activity of haeme oxygenase was highly elevated (at 16 h). Furthermore, a change in liver content of glutathione (GSH) (depletion followed by a rebound) was shown in the study after administration of potassium hexachloroplatinate(IV) and when Pt^{2+} and Pt^{4+} was administered as a complex with glutathione their abilities to perturb haeme metabolism (e.g. haeme oxygenase activity) was blocked (86). The biosynthesis of haeme was also affected in different ways after administration of potassium hexachloroplatinate(IV). The activity of delta-aminolevulinic acid synthetase (ALAS) in the liver and kidney was decreased for about 12 h and then increased (86, 117). Reduced activities of other enzymes regulating haeme biosynthesis in the kidney (delta-aminolevulinic acid dehydratase, uroporphyrinogen I synthetase, ferrochelatase) was also found (at 24 h) and the total porphyrin content of kidney (at 24 h) was markedly decreased (117).

Effects on drug metabolism was shown in a study with male Sprague-Dawley rats (51). The intraperitoneal injection of platinum(IV) chloride for two consecutive days, at a dose of 18.9 mg/kg bw/day (56 μmoles/kg bw/day; 10.9 mg Pt/kg bw/day) increased hexobarbital-induced sleeping time by approximately 50% ($p<0.05$) and significantly decreased some parameters of drug metabolism measured in hepatic microsomes (decrease in cytochrome P450 and cytochrome b_5). A small decrease in the parameters of drug metabolism (significant decrease in aminopyrine demethylase) and a small increase in sleeping-time was noted already at a concentration of 4.7 mg/kg bw/day (14 μmoles/kg bw/day; 2.7 mg Pt/kg bw/day). When soluble platinum salts (platinum(IV) chloride and platinum(IV) sulphate) were administered in the diet or via drinking fluid for 1, 4 or 13 weeks there was a general pattern concerning the parameters of drug metabolism: after 1 week of administration there was a decrease (or no alterations) in these parameters, while there was an increase (or no alterations) after 4 or 13 weeks. For example treatment for 1 week with platinum(IV) sulphate at a concentration of 750 mg/L drinking fluid (1.6 mmol/L about 60 mg Pt/kg bw/day) caused a

decreased activity ($p<0.05$) of aniline hydroxylase, while significant increases in aniline hydroxylase or cytochrome b_5 were observed when platinum(IV) chloride was administered for 4 weeks at a dose level of 4.5 g/kg diet (13.2 mmol/kg diet) corresponding to about 230 mg Pt/kg bw/day (total dose 1.58 g Pt /rat) or for 13 weeks at a dose level of 0.2 g/L (0.54 mmol/L; total dose 1.4 g Pt/rat or about 16 mg Pt/rat/day). Platinum(IV) oxide had marginal effects on the measured parameters even at a dose level of 6.8 g/kg diet (29.8 mmol/kg diet; 4.9 g Pt/rat during the 4 week treatment), which would correspond to about 700 mg Pt/kg bw/day (50, 51).

Inhibition of DNA synthesis as measured by the incorporation of radioactive thymidine, consistent with an inhibition of DNA polymerase according to the authors, also was found in one study in male Sprague-Dawley rat with platinum(IV) chloride (36). Thymidine incorporation in the spleen was reduced by one third at intraperitoneal injection of a dose of 4.7 mg/kg bw (14 μmol/kg bw; corresponding to 2.8 mg Pt/kg bw), while a decrease in thymidine incorporation in other tissues (kidney, liver, testis) was found at higher dose levels.

11. Observations in man

11.1. Effects of single exposure

There are few reports of acute poisoning after exposure to platinum/platinum compounds in man. Hardman and Wright 1896 (44) reported the death of a child aged 7 months who died five hours after the accidental administration of 8 gram of potassium tetrachloroplatinate(II). A non-fatal case of platinum poisoning after oral ingestion also has been described. A 31 year-old man ingested 600 mg of potassium tetrachloroplatinate(II) suspended in a 10 ml solution in a suicide attempt. After 12 hours he complained of nausea, vomiting, diarrhea, and leg cramps. Subsequent medical examination revealed acute renal failure with little urine output, mild hepatitis, fever, gastroenteritis, mild metabolic acidosis, leukocytosis, and eosinophilia. The initial serum platinum concentration was 245 μg/dl and his spot urine platinum concentration was 4200 μg/L. All symptoms and signs of toxicity resolved within six days (180).

11.2. Effects of repeated exposure

Occupational exposure to platinum salts is a well-known cause of respiratory allergic manifestations and skin reactions (20, 54, 124, 135). The symptoms include lacrimation with burning and itching of the eyes, irritation of the upper respiratory tract, running of the nose, sneezing, coughing, tightness of the chest, wheezing and shortness of breath, as well as angioedema, urticarial and eczematous skin lesions, usually on exposed areas (27, 59, 69, 87, 120, 131). However, true allergic contact dermatitis from exposure to platinum compounds is rare and the dermatitis occasionally seen sometimes may be of a primary irritant nature e.g.

following exposure to strong acids and alkalis (20, 35, 58, 64, 84, 147). The compounds mainly responsible for sensitisation are hexachloroplatinic(IV) acid and chlorinated salts such as ammonium hexachloroplatinate(IV), ammonium tetrachloroplatinate(II), potassium hexachloroplatinate(IV), potassium tetrachloroplatinat(II) and sodium hexachloroplatinate(IV)) (20, 38, 59, 87, 120, 124, 127, 135). Metallic platinum is not associated with hypersensitivity, although a single case of dermatitis due to a platinum ring has been reported (147).

The latency period from the first exposure to platinum compounds to the occurrence of the first symptoms of a hypersensitivity disease varies between one week and more than 20 years**,** but sensitisation usually develops within a few months to a few years (31, 58, 94, 95, 119, 120, 125). The symptoms tend to become worse upon continued exposure and sensitised individuals usually are never asymptomatic in a platinum-containing atmosphere (38, 59, 93, 120, 131). When the subjects are removed 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 (84, 131). Furthermore, a nonspecific airway hyperreactivity may persist (7, 23, 93).

The particular effects attributable to platinum salts were first noted by Karasek and Karasek (1911; cited in 58, 64) who examined workers in 40 photographic studios in Chicago and found eight persons who complained of irritation of the nose and throat with accompanying sneeezing and coughing. Bronchial irritation with difficulties in breathing was so severe in some cases that they were unable to use paper treated with potassium chloroplatinate. Dermatitic skin lesions were also noted during this study. Since then there have been numerous case reports relating e.g. rhinitis, conjunctivitis, cough, asthma and urticaria to exposure of hexachloroplatinic acid/complex salts of platinum in industry (mainly in workers and chemists engaged in the refining of platinum), but no air concentrations are given in the studies (38, 64, 69, 81, 83, 87, 97, 120, 142, 167, 185).

The first occupational survey of platinum refinery workers, where measurements of the platinum content of the air were made, was published in 1945 by Hunter et al (59). They investigated all the workers 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, 52 (57%) had the asthmatic syndrome to some degree (suffered from sneezing, running of the nose, tightness of the chest, shortness of breath, cyanosis, wheezing and cough), when they were in the factory and for about one hour after they had left. 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 did occur also in those engaged on certain parts of the wet processes, where droplets of the complex salts were present in the atmosphere. The platinum content of the refinery atmosphere was estimated at various points and during various operations with figures ranging from 0.9 $\mu g/m^3$ to 1700 $\mu g/m^3$ (table 7). 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 experi-

enced 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 apparent in the workers exposed to metallic platinum dust only, in any of the factories, despite that the sieving of spongy platinum produced a high concentration of platinum in the atmosphere (400 to 960 $\mu g/m^3$).

In some other early studies in refinery workers exposed to platinum salts the occurrence of symptoms has been even higher (Table 13). In a five-year study of employees in a platinum refinery in the USA all workers exhibited some degree of inflammatory changes in the conjunctivae and the mucous membranes of the upper respiratory tract, while 60% (12/20) 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 8 of these had a positive skin test (131). In a French study (120) the prevalence of respiratory and/or cutaneous manifestations was 69% (35/51) and the symptoms occurred mostly at night and in accession to work. In two German studies work-related symptoms such as sneezing, coughing, asthma, urticaria and eczema were found in 73% (8/11; 4 workers with symptoms had been removed and were not included) and 88% (14/16) (89, 138). However, skin tests were not generally performed in two of the three latter studies (89, 120). In the third study (138) 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. No relevant measurements of the content of platinum in the air were done in any of the studies (89, 120, 131, 138). In a report from 1975 (45) it was stated, that nasal ulceration was found in 8 of 16 workers (had proceeded to perforation of the septum in one case) exposed to ruthenium and platinum salts during surface coating of anodes (include heating to 400-600°C) and that one other worker had suffered from a severe asthmatic attack. The case of asthma was attributed to exposure to platinum salts, but because of the absence of reports of nasal ulceration with platinum salts it was considered by the author that the nasal ulceration and perforation described were due to ruthenium salts rather than platinum salts. No exposure data were given in this study.

In a more recent Chinese study (149) the prevalence of allergic/irritative symptoms was reported to be very high. For example skin lesions (characterized as pruritus with face rashes) and/or mucosa irritation (running of the nose, sneezing, irritant pain and running of the eyes) were found in 20 of the 23 examined workers, but the total number of workers exhibiting symptoms was not given. Skin patch test with sodium chloroplatinate was positive in nine cases, who accepted a 0.0075% test solution. Air samples taken at various points of the refinery showed that the workers were exposed to extremely high levels of dust or spray of complex platinum salts (5-80 mg/m^3; at most points <10 mg/m^3), but no close relationship between the air levels and the incidence of symptoms was found. However, none of these symptoms occurred in the workers exposed only to metallic platinum dust or spray.

In a historical prospective cohort study (170) 91 workers (57 smokers) in a UK platinum refinery who started work in 1973 - 1974 was followed up until 1980. Forty-nine/ninety-one (54%) reported respiratory symptoms and 22 of those developed a positive skin prick test result to platinum salts. Smokers were found to have an increased risk of sensitisation by platinum salts: smoking was the single most important predictor of a positive skin test result to platinum salts (the risk was 4-5 times that in non-smokers) and consumption of cigarettes was the single most important predictor of symptoms (the risk was about twofold greater). The risk from atopy was smaller than that for smoking and was not significant after taking account of smoking. One third of the workers were considered as atopics, but it was stated, that people with a history of allergy were not employed in the refinery. In an earlier abstract, a preliminary study of the 1973-1974 cohort was presented (31). The results showed that 35/86 (41%) developed disease and all cases appeared within two years of starting exposure. Of the 35 subjects affected, 24 developed positive skin prick tests to platinum salts, while there were no positive reactions in those unaffected (31). The air level of platinum was not given in any of the references (31, 170).

In a large scale refinery survey published in 1986, 306 South African platinum refinery workers accepted for employment on grounds of absence of evidence of atopy were investigated. Thirty-eight (12.4%) had a positive skin prick test to platinum halide salts (107), but there were no data on number of workers with platinum allergy related symptoms or air levels of platinum.

The prevalence of bronchial asthma and dermatitis was measured in a group of 16 Japanese workers engaged in the manufacture of platinum-coated oxygen sensors (148 cited in 56). Measurements of the concentrations of Pt in the air ranged from 0.14 to 1.83 $\mu g/m^3$ (48-hour averages of 0.46 and 1.1 $\mu g/m^3$), but the work was said to involve intermittent exposures to concentrations of ammonium hexachloroplatinate(IV) higher than those in the workplace as a whole (e.g. during cleaning of sensors). Results showed that 2/16 (12.5%) workers had severe work-related bronchial asthma and gave positive reactions on topical challenge with 1% hexachloroplatinic(IV) acid solution. Among the remaining workers 11/14 showed contact dermatitis, 6/14 showed pharyngeal irritation and 2/14 was said to suffer from nasal obstruction, sneezing and coughing. Seven of the workers gave positive reactions on topical challenge with 1% hexachloroplatinic(IV) acid. It was also stated that pulmonary function tests and haematological measurements showed no abnormalities. The prevalence of contact dermatitis in the study is very high and might point to exposure to other compounds as well.

In a large investigation in the USA (7, 14, 23), 107 (87%) of 123 available current workers and 29 former workers (suspected platinum salts allergy stated as the reason for termination) in a plant, that reclaimed platinum and other precious metals from scrap metals and consumed catalysts in 1981, were investigated. 65% of the current and 97% of the terminated workers were smokers/ex-smokers. Rhinitis was noted in 44% current and 34% terminated workers, asthma was reported in 29% and 48%, respectively 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 and the reactions in the current workers mostly occurred at concentrations ranging between 10^{-6}-10^{-3} g/ml, while the terminated workers showed reactions at lower concentrations (10^{-9}-10^{-6} g/ml) (23). Sensitisation to platinum salts occurred among workers in all areas of the facility except the administrative offices. Platinum salts sensitivity generally varied directly with the environmental air concentrations of platinum salts in the employees´ present work areas and the risk of demonstrating platinum salts skin test reactivity was calculated by the authors to increase 13% per 1 μg/m^3 increment in work area air concentration of platinum salts ($p<0.01$) (7). A positive skin prick test (platinum salts) was found for 67% of the workers (2/3) in the tray room, where the mean air concentration was 27.1 μg/m^3, but only for 14% (2/14) of the employees in other areas of the refinery (mean air concentration 10.7 μg/m^3). 11% (2/19) of the workers in the analytical laboratories, where the mean air concentration was 0.4 μg/m^3 (and the air measurements of platinum salts never exceeded 2.0 μg/m^3) showed a positive skin prick test. No correlation between air levels and symptoms was presented, but skin test reactivity to platinum salts was significantly associated with increased prevalences of rhinitis symptoms, asthma symptoms, 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 platinum salts sensitisation was not found to be associated with atopic tendency. An important observation was the high prevalence of symptoms consistent with allergic conditions (e.g. positive cold air challenge, $FEV_1/FVC<70\%$) among former workers with a persistent positive platinum skin prick test and with no apparent platinum salts exposure during an average of five years since termination (7). Analysis of company environmental monitoring data for 1977 to 1979, providing over 75 air measurements of platinum salts, showed that the air levels in the refinery, recovery and warehouse areas exceeded 2 μg/m^3 (geometric means of 8-hour TWA levels) between 50 and 75% of the time (Table 7) (7, 23).

The occurrence of a persistent positive skin prick test as well as a nonspecific airway hyperreactivity was also shown in a late German study on 24 refinery workers (15 smokers/ex-smokers) examined on two occasions. It was found, that most individuals with an immediate-type asthma caused by platinum salts maintained a nonspecific airway hyperreactivity for many months (1-77 months) after removal from exposure. Although about one-third of the subjects ceased to have asthmatic symptoms during the study period, there was no change in FEV_1, or bronchial hyperresponsiveness, nor was this the case with skin reactivity or bronchial responsiveness to platinum salt (skin prick tests with platinum salt became negative in three subjects, but this was not accompanied by decreasing bronchial responsiveness to methacholine or platinum salt) (93). These results are in contrast to the results found in an unpublished British study (Newman-Taylor, 1981 cited in 56). In this study the prevalence of respiratory symptoms and skin sensitivity (skin prick test) to ammonium hexachloroplatinate(IV) was determined in former workers of a platinum refinery. The study population consisted of 109 individuals, 36 of whom had ceased employment due to the development of platinum salt-related asthma

(33%). Twenty-nine of the formerly Pt salt-sensitive and 41/73 of the non-sensitised former workers participated in the follow-up study. Results showed no statistically significant differences in pulmonary function tests (FEV_1, FVC, cold air reactivity) and no difference in the reporting of shortness of breath and chest tightness between the formerly sensitised and non-sensitised subjects. The formerly sensitised workers reported a greater prevalence of shortness of breath on exertion, but this was judged to be of doubtful clinical significance. Twenty-seven of the 29 Pt salt-sensitive individuals had shown positive skin prick test at the time of leaving employment, but only one worker still showed positive results at follow-up.

Today, when the air level of soluble platinum salts in industry generally is much lower than some decades ago, platinum sensitivity is expected to be rare. However, the above mentioned recent German study (93) indicates that this is not always the case. Two other German studies (21, 95) support this finding. In one study (21) all 65 workers of the platinum-processing departments of a chemical plant were investigated with regard to the prevalence to allergic respiratory tract diseases. The mean duration of exposure to platinum was 8.9 years (range 1-40 years). The occurrence of conjunctivitis, rhinitis, coughing, expectoration or dyspnea related to work was reported by 15 subjects (23%) and these symptoms were found more frequently in the staff with high platinum exposure than in persons with moderate of low exposure ($p<0.01$). Fifty-two per cent of the workers in this group suffered from work-related symptoms, compared to 4% and 14% in the other two groups. The same symptoms without a strict relation to the workplace were reported by 10 workers. 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 ($p<0.05$) fall in FEV_1 from 100.7% to 95.9% of the predicted values. The FEF_{25} flow values fell markedly from 95.1% to 73.4% ($p<0.05$), but the resistance remained unchanged. In the group with symptoms not related to work no significant changes in lung function were found. Sixty-four of the workers also were skin prick tested. A positive cutaneous reaction with K_2PtCl_6 was found in 12 employees (18.7%). A positive result was obtained significantly more frequently in the group with work-related symptoms of respiratory allergy (9/14) than in the other groups (2/10; 1/40). 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 total dust in the separation shop in 1984 (each over 3.5 h) revealed an air concentration of <0.2 $\mu g/m^3$ (detection limit) and in 1986 (over 2 h) showed concentrations of 0.08 and 0.1 $\mu g/m^3$. Two personal air monitorings in filter press workers for 1 h in 1986 revealed platinum salt concentrations in total dust of <0.05 $\mu g/m^3$ (detection limit). Furthermore, it was stated that the German OEL (2.0 $\mu g/m^3$) was maintained over the long term. Otherwise no exposure data were presented in the study.

In another study (94, 95) 24/27 subjects working in a platinum refinery and 6 former workers (two workers with recurrent sporadic platinum exposure; four workers with 7, 9, 45 and 96 months since cessation of exposure) were investigated. Two of the current workers (8%) and all the former workers suffered from work-related symptoms, that is 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-six of the 30 workers allowed skin prick test and 10 of these had positive reactions: all workers from the group with work-related symptoms (except one worker who did not allow skin prick test) and three workers from the group with doubtful work-related symptoms (including the worker who developed work-related asthma after the study). Smoking was not found to increase the risk of developing platinum salt allergy, 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) than did workers of the other study groups (score points 1.9 and 1.8), but the exposure level was merely judged by the production manager (graded into 1-3 score points). The drying process of the salts was designated as one of the most dangerous processes (95). In a late report one of the authors (92) shortly presented an investigation on 261 workers in a company producing catalysts, followed for at least 2.5 years (1989-1992). The air levels were considered in general to be lower than in platinum refineries, but no data on the measurements were given. It was found that four workers suffered from platinum salt allergy at the first investigation and four other workers developed the disease later (totally 3%). No cases of allergy were found in areas where the exposure level of soluble platinum compounds were below 0.01 $\mu g/m^3$. However, the short duration of the study and the lack of details concerning the number of employees exposed to different concentrations of platinum salts should be noted.

In a pilot study (173), 21 men exposed to platinum metal dust for 6 weeks to 12 months during work with car catalysts (including recycling) and mechanical treatment of platinum in a workshop was examined to detect signs of platinum allergy. No data supporting the occurrence of platinum sensitivity was found, but no details were given in the study. The air levels of platinum were 1.7-6.0 $\mu g/m^3$ (around 6 $\mu g/m^3$ during cutting and sawing).

11.3. Genotoxic effects

Data have not been found.

Table 13. Prevalence of symptoms and positive skin tests in workers exposed to soluble platinum salts

Total workers[a]	Workers with symptoms[b]	Prevalence of symptoms (%)[c]	Air concentration of platinum (μg/m^3)	Ref
91 (16)	52 (4)	57 (25)	0.9-1700	59
20 (19)*	12 (8)	60 (42)	nd	131
11 (nd)	8 (nd)	73 (nd)	nd	89
16 (-)	14 (-)	88 (-)	-	138
51 (nd)	35 (nd)	69 (nd)	nd	120
91 (84)**	49 (22)	54 (26)	nd	170
107 (107)	28***46****(15)	29*** 44**** (14)	>2	7, 14, 23
24 (20)	2 (4)	8 (20)	<0.08	94, 95
65 (64)	15 (12)	23 (19)	<0.1, <2.0	21

[a] Values in parentheses are numbers of skin-tested workers.
[b] Values in parentheses are numbers of workers with a positive skin test.
[c] Values in parentheses give positive skin tests as a percentage of skin-tested workers.
*Findings made within five years.
**historical prospective cohort study
***asthma
****rhinitis
nd= not determined

11.4. Carcinogenic effects

Reports of cancer related to occupational exposure to platinum compounds have not been found (34, 73, 108).

12. Dose-effect and dose-response relationships

There are no reports concerning other effects than allergy and irritation (skin and mucous membranes) in humans occupationally exposed to soluble platinum salts and data on the potential health effects in humans arising from exposure to platinum metal or insoluble platinum compounds are completely lacking. Furthermore, there are difficulties in establishing a dose-effect and dose-response relationship, since there are wide variations in measured air levels of Pt (Table 7) and most workers have changed their activities several times during their occupational exposure time. However, in a few studies the exposure level to some extent has been related to the prevalence of symptoms or positive skin prick test results and in one study a bronchial provocation test was used to correlate dose and effect. These studies are briefly described below.

In a study on 107 platinum refinery workers (out of 123) the correlation between air concentrations of platinum salts in the employees present work area and the prevalence of platinum salts skin sensitisation suggested an exposure-response relationship between the level of exposure and the prevalence of allergy (7, 14, 23). The company´s environmental monitoring data for 1977 to 1979 providing over

75 air measurements of platinum salt (geometric means of 8-hour time weighted average air levels) were available for analysis and the risk of demonstrating platinum salts skin test reactivity was calculated by the authors to increase 13% per 1 $\mu g/m^3$ increment in work area air concentration of platinum salts ($p<0.01$). A positive skin prick test (platinum salts) was found for 67% of the workers (2/3) in one part (tray room) of the refinery, where the mean air concentration was 27.1 $\mu g/m^3$. A positive skin prick test was also found for 14% (2/14) of the employees in other areas of the refinery where the mean air concentration was 10.7 $\mu g/m^3$. None of the office workers (0/15) was sensitive to platinum salts, whereas 11% (2/19) of the workers in the analytical laboratories showed a positive skin prick test. The mean air concentration of platinum in the air conditioning unit (supplying air to the administrative offices of the facility) and in the analytical laboratories were 0.6 $\mu g/m^3$ and 0.4 $\mu g/m^3$, respectively. The air measurements of platinum salts in these areas never exceeded 2.0 $\mu g/m^3$. No correlation between air levels and symptoms was presented, but platinum salt sensitisation was significantly associated with increased prevalences e.g. of rhinitis symptoms, asthma symptoms and reported dermatitis.

The prevalence of allergic respiratory tract diseases in all 65 employees of the platinum-processing departments of a German chemical plant was reported in another study (21). It was found that 15/65 (23%) of the workers suffered from work-related symptoms of respiratory allergy and 12/64 (19%) had a positive skin prick test to platinum salts. Work-related symptoms were significantly more frequent in the staff with high platinum exposure than in persons with moderate or low exposure ($p<0.01$). Thus, 52% of the workers in this group suffered from work-related symptoms, compared to 4% and 14% in the other two groups. A positive skin prick test was also obtained significantly more frequent in workers with work-related symptoms of respiratory allergy, than in other workers. 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. However, two stationary air monitorings in total dust in the separation shop in 1986 over 2 hours showed concentrations of platinum salts of 0.08 and 0.1 $\mu g/m^3$, and 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 was also stated that 2.0 $\mu g/m^3$ was maintained in the plant over the long term. Otherwise no exposure data were presented in the study.

In a study on 24 subjects (24/27 participated) working in another German platinum refinery the prevalence of clearly work-related asthmatic/upper respiratory tract symptoms was only 2/24 (8%), but one worker with doubtful work-related symptoms (rhinitis and a positive skin prick test with $PtCl_6^{2-}$) developed work-related asthma five months after the study and further two workers belonging to the group with doubtful work-related symptoms showed a positive cutaneous reaction with $(PtCl_6)^{2-}$ (20 current workers were skin prick tested and 20% showed a positive test). The only symptom they experienced was rhinitis which occurred regularly after exposure, but also at home, and did not disappear during weekends (94, 95).

Workers with work-related symptoms were considered to have a higher exposure to platinum salts (score points 2.5) than did workers of the other study groups (score points 1.9 and 1.8), but the exposure level was merely judged by the production manager (graded into 1-3 score points) and air levels of Pt were not given for any of the groups. Platinum salt exposure in the different working areas had been measured by the refinery and was stated to be generally below 0.08 $\mu g/m^3$ (no exposure data were presented). In a later report one of the authors (92) shortly presented an investigation on 261 workers in a company producing catalysts (1989-1992). The air levels were considered as lower in general, than in platinum refineries, but data on the measurements were not given. It was found that about 3% of the workers developed platinum salt allergy, but no cases of allergy were found in areas where the exposure level of soluble platinum compounds were below 0.01 $\mu g/m^3$. The short duration of the study and the lack of details concerning the number of employees exposed to different concentrations of platinum salts preclude definite conclusions on the risk of developing sensitisation reactions.

When bronchial provocation test with platinum salt was performed on 27/35 former platinum refinery workers with work related symptoms, 22 of these showed a fall of 50% or more in specific airway conductance, whereas none of the controls showed any reaction (94). It was calculated by the authors, that at the occupational exposure limit (OEL) value of 2 $\mu g/m^3$ workers inhale about $2.0x10^{-8}$ g/minute or $0.5x10^{-10}$ mol/minute and that this corresponds to the provocation dose causing 50% fall in specific airway conductance (PD_{50}sGaw) in bronchial provocation tests with platinum salt; however, details of how the calculations are made are lacking. The authors concluded, that in a number of countries legal OEL values for occupational platinum salt exposure bear risks for those workers who are sensitised to platinum salt.

There are few inhalation studies of platinum compounds in animals. In one study (17) signs of bronchial hyperreactivity (serial bronchoprovocation challenges with increasing concentrations of the platinum salt) was found in monkeys after intermittent exposure for 12 weeks to sodium hexachloroplatinate(IV) at the exposure level of 200 $\mu g\ Pt/m^3$, but not at the exposure level 2000 $\mu g\ Pt/m^3$. (Significant impairments in pulmonary function was also shown in control animals after challenge with the highest concentration of the platinum salt). However, in a later study (16) exposure to about 200 $\mu g/m^3$ ammonium hexachloroplatinate(IV) had no significant effects on postexposure Pt or methacholine reactivity in monkeys. Furthermore, there were no overt ill effects or significant differences in body weights, but the study was designed to detect differences in immunologic parameters and effects in the airways. There are other studies in animals in which platinum compounds are administered in other ways. The results of some of these studies are summarised in Table 14.

Table 14. Some dose-effect data for animals exposed to soluble platinum compounds

Exposure	Species	Effect	Ref
H_2PtCl_6: 40-50 mg/kg bw (15-19 mg Pt/kg bw*) ip, single dose	male rat (F344 Fischer CDF)	LD_{50}, renal failure, histopatol lesions in kidney, thymus	171
$PtCl_4$: 27 mg/kg bw (0.08 mmol/kg bw; 15.6 mg Pt/kg bw) intra-testicular, single dose	rat (albino)	decreased testis weight, testicular necrosis with destruction of spermatozoa	70
$Pt(SO_4)_2x4H_2O$: 750 mg/L drinking-water for 8 days; total intake 60 mg Pt/rat (about 140 mg/kg bw/day or 59 mg Pt/kg bw/day)	male rat (Sprague-Dawley)	reduced weight gain, decreased activity of aniline hydroxylase	50, 51
$PtCl_4$: 550 mg/L drinking-water for 29 days; total intake 250 mg Pt/rat (about 74 mg/kg bw/day or 43 mg Pt/kg bw/day)	male rat (Sprague-Dawley)	increase in relative kidney weight, reduced weight gain	50
$PtCl_4$: 50 ppm Pt in the diet for 4 weeks; total intake 21 mg Pt/rat (about 8.6 mg/kg bw/day or 5 mg Pt/kg bw/day)	male rat (Sprague-Dawley)	sign increase in plasma creatinine; decrease in erythrocyt count, haematocrit	130
$PtCl_4$: 0.9 mg/kg bw/day (0.08 mmol/kg bw tot dose; 0.52 mg Pt /kg bw/day) sc, 30 days	mouse (Swiss)	decreased testis weight, spermatogenic arrest	70

*molecular weight counted on the hexahydrate

13. Previous evaluations by (inter)national bodies

Recently, the UK Health and Safety Executive (HSE) has published a criteria document on platinum metal and soluble platinum salts. Their conlusions were: A number of studies have provided clear evidence that exposure to the platinum chloride salts leads to skin and respiratory hypersensitivity in humans. The available data do not allow conclusions to be drawn as to whether or not a threshold for respiratory sensitisation exists. No data are available on the potential health effects in humans arising from exposure to platinum metal or insoluble platinum salts. The lack of any documented cases of allergy suggests that it is unlikely that platinum metal is capable of eliciting the skin and respiratory health effects associated with soluble platinum salts. A summary of the animal studies show, that some platinum salts may produce irritation of skin, eye and respiratory tract. The genotoxic potential of platinum salts has not been systematically investigated, but from the limited data available it appears that some soluble platinum salts are mutagenic in vitro, although this potential has not been demonstrated in vivo.

The conclusions of the International Programme on Chemical Safety (IPCS) in 1991 on health effects of platinum and platinum compounds were: By far the most significant health effect from exposure to soluble platinum salts is sensitisation. Some halogenated platinum salts are highly allergenic in humans. There is no evidence for sensitisation from metallic platinum, except for one unsubstantiated case of contact dermatitis. The present occupational exposure limit (2 $\mu g/m^3$) might not be sufficient to prevent platinum salt hypersensitisation, although it is difficult to reach a firm conclusion because of the lack of adequate data. To minimize the risk, workplace exposure should be as low as practicable. No data are available to assess the carcinogenic risk of platinum or its salts to humans.

14. Evaluation of human health risks

14.1. Groups at extra risk

There are only limited data to quantify workplace exposure. However, occupational exposure to the soluble, halogenated platinum compounds, known to be responsible for sensitisation, is mainly found during primary refining of platinum, during catalyst manufacture and when platinum is reclaimed from scrap metal and expended catalysts.

Smokers seem to be more susceptible to the sensitising effects of platinum salts, whereas this cannot be clearly judged for the atopic status (7, 23, 170; Linnett, 1985, cited in 84). A correlation between atopy and allergy for platinum compounds is indicated in some early studies (108), but there might be confounding factors e.g. smoking. In more recent studies atopy has not been correlated to platinum sensitivity. This may be due to pre-employment screening and to small study populations (7, 21, 58, 170). However, preemployment screening and exclusion of atopics will never solve the problem since allergy to platinum salts also occurs to a large extent in nonatopics. Furthermore, atopy is very common, and decisions made because of atopy probably affect about one third of the working population. Thus, prevention should focus on environmental control (112, 169).

14.2. Assessment of health risks

The most significant health risks from occupational exposure to soluble platinum salts are respiratory sensitisation and skin effects. There is scarcely any information of the health effects in humans arising from exposure to platinum metal, but it is unlikely that platinum metal is capable of eliciting the allergic reactions associated with some soluble platinum salts, since no cases of respiratory health effects attributed to platinum metal are known and only one single case of contact dermatitis has been reported.

The prevalence of respiratory/cutaneous symptoms among refinery workers exposed to platinum salts has been very high - frequently over 50% - and sometimes the disease has developed very rapidly (59, 89, 120, 131, 138, 170). The

exposure conditions have improved during the last decades and the prevalence of work-related symptoms in some later studies was lower (8-23%), but still positive skin prick tests to platinum salts were obtained in about 20% of the tested workers (21, 94, 95). A correlation between the prevalence of work-related symptoms and exposure level of platinum salts has been stated in a few studies (21, 94, 95). However, few exposure data are presented and the importance of peak exposures of short duration for sensitisation cannot be evaluated on the basis of existing data. In one study (7, 14, 23) the risk of demonstrating platinum salts skin test reactivity (skin prick test) was calculated by the authors to increase 13% per 1 $\mu g/m^3$ increment in work area air concentration of platinum salts.

In many cases the respiratory/cutaneous reactions following exposure to platinum salts has been shown to be IgE-mediated. Specific sensitisation has been demonstrated in skin prick tests with a range of 12-26% in later studies (7, 14, 21, 23, 94, 95, 107, 170). Indications of the potency of the soluble halogenated salts of platinum are, that with a typical delivery of $3x10^{-6}$ ml solution into the epidermis, a salt concentration of 10^{-9} g/ml (according to the authors) is sufficient to elicit a positive reaction in sensitised skin (27, 108, 124) and the fact that concentrations of 1 μg/ml potassium hexachloroplatinate(IV) intradermally have caused anaphylactic reactions (27, 38). Furthermore, if the workers are exposed to low levels of other irritant or toxic gases and fumes as well (e.g. chlorine, hydrogen chloride**,** nitric acid and ammonia), this may possibly potentiate the effects of platinum salt exposure (7, 13, 16, 84). However, respiratory and cutaneous symptoms are not always due to specific sensitisation and thus non-allergic mechanisms and irritative effects also should be born in mind (152). It has been postulated that the dermatitis occasionally seen among refinery workers sometimes are of a primary irritant nature e.g. following exposure to strong acids and alkalis (20, 35, 58, 64, 84, 147). In addition to the platinum-specific respiratory reactions, an unspecific bronchial hyperreactivity that may persist for years after exposure has ceased has also been shown in some studies (7, 23, 93).

There are no reports of other effects of platinum compounds than allergy/irritation of the respiratory tract and skin after occupational exposure. Nausea, vomiting, diarrhea, and leg cramps was described in one case after ingestion of 600 mg of potassium tetrachloroplatinate(II). Subsequent medical examination revealed acute renal failure, mild hepatitis, mild metabolic acidosis and gastroenteritis (180). In animal experiments some platinum salts have been shown to produce irritation of skin, eye and respiratory tract. Effects e.g. on kidney, testis, blood and thymus have been observed after peroral, subcutaneous or intraperitoneal administration of hexachloroplatinic acid/soluble platinum salts, at dose levels corresponding to air levels much higher than present work place exposure levels. Many platinum salts/complexes have been shown to be mutagenic in vitro, but the genotoxicity of platinum compounds (except platinum containing drugs) is not very well investigated and it is not possible from the available studies to draw firm conclusions regarding the risk from exposure to platinum compounds in the work environment.

14.3 Scientific basis for an occupational exposure limit

In the occupational setting where inhalation exposure is dominating, the critical effects of soluble platinum salts are those related to the respiratory tract, whereas no critical effects can be established for platinum metal or insoluble platinum compounds. Some of the halogenated complex salts of platinum are potent respiratory sensitisers in human and only small amounts of the compounds might be needed for induction of sensitivity, but the amounts required to elicit reactions are far lower. Thus even very low OEL values may be inadequate for prevention of reactions in already sensitised subjects and there are clear indications that 2 $\mu g/m^3$ - the legal occupational exposure limit used in a number of countries - is not sufficiently low to protect the workers from elicitation of allergic symptoms (7, 14, 21, 23, 92, 95). It is difficult to establish a LOAEL, because few exposure data are available and are poorly reported (see Section 12); however, a LOAEL may be as low as 0.08-0.1 $\mu g/m^3$ (21, 95). Existing data on exposure-response relationships do not allow the identification of a NOAEL for soluble platinum salts. It should be noted, that peak exposures of short duration occur, which may be of importance for the induction of sensitivity.

15. Research needs

One problem in assessing the risk of humans from exposure to platinum is the analytical problems and the definition of reference values (baseline concentrations) in blood, urine and tissues. The absence of adequate reference values makes it difficult to establish relationships between element concentrations, toxic effects and air levels.

There is also a need for more information on possible genotoxic effects. The antineoplastic agent cisplatin and some analogues bind to DNA and are mutagenic. A few antitumor cis-platinum(II) coordination complexes (including cisplatin) also have been shown to be carcinogenic in animal studies. The mutagenicity and carcinogenicity of other platinum compounds is less well investigated, but due to differences in chemical reactivity (lability of ligands, number of active sites etc) it is reasonable to expect that not all forms of platinum pose this hazard. However, many platinum salts/complexes have been shown to be mutagenic in vitro and thus further investigations e.g. animal studies, cytogenetic tests and well performed epidemiological studies would be of interest.

16. Summary

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

The most significant health risk from occupational exposure to soluble platinum compounds is sensitisation of the airways. It is during the production and handling of hexachloroplatinic acid and certain complex halogenated salts of platinum, allergic symptoms involving the respiratory tract and the skin have occurred. Smokers seem to be more susceptible to the sensitising effects of platinum salts, whereas this cannot be clearly judged for the atopic status. Elicitation of allergic symptoms occur at Pt air levels below 2 ug/m^3, possibly at Pt levels as low as about 0.1 ug/m^3. Platinum metal is not associated with allergy. There are no reports of other effects of platinum compounds than allergy/irritation at occupational exposure. 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.

Keywords: allergy, asthma, health effects, irritation, occupational exposure limit, platinum, platinum salts, refinery, review, rhinitis, risk assessment

17. Summary in Swedish

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

Den mest signifikanta hälsorisken vid yrkesmässig exponering för lösliga platinaföreningar är sensibilisering av luftvägarna. Det är vid produktion och hantering av hexakloroplatinasyra och vissa halogenerade platinakomplexsalter, som allergiska symptom i luftvägar och hud har rapporterats. Rökare förefaller vara mer mottagliga för platinasalters sensibiliserande effekter, medan ett samband med atopi inte har klarlagts. Allergiska symptom kan utlösas vid Pt lufthalter lägre än 2 ug/m^3, möjligen vid så låga halter som c:a 0.1 ug/m^3. Platinametall har inte associerats med allergi. Det finns inga rapporter angående andra effekter av platinaföreningar vid yrkesmässig exponering än allergi/irritation. Många platinasalter/komplex är mutagena in vitro, men det är inte möjligt att dra slutsatser från tillgängliga studier angående genotoxisk risk i arbetsmiljön.

Nyckelord: allergi, astma, hygieniskt gränsvärde, hälsoeffekter, irritation, platina, platinasalter, rinit, riskbedömning, smältverk, översikt

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Appendix 1a.

Permitted or recommended maximum levels of platinum (metal) dust in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark		1		1994	1
Finland	1			1996	2
Germany		-		1996	3
Iceland		-		1989	4
Netherlands		1		1996	5
Norway		-		1995	6
Sweden		-		1996	7
USA (ACGIH)		1		1996	8
(NIOSH)		1		1994	9
(OSHA)		-		1994	9

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Appendix 1b.

Permitted or recommended maximum levels of soluble platinum salts (as Pt) in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark		0.002		1994	1
Finland		0.002		1996	2
Germany		0.002	Chloroplatinum ceiling; S	1996	3
Iceland		-		1989	4
Netherlands		0.002		1996	5
Norway		0.002		1995	6
Sweden		-		1996	7
USA (ACGIH)		0.002		1996	8
(NIOSH)		0.002		1994	9
(OSHA)		0.002		1994	9

S = risk for sensitisation

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