1997:14

DECOS and NEG Basis for an Occupational Standard

Platinum

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Nordic Council of Ministers

ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE
ISBN 91–7045–420–5 ISSN 0346–7821

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ISBN 91–7045–420–5
ISSN 0346-7821
Tryckt hos CM Gruppen

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.

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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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Submitted for publication June 12, 1997.

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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