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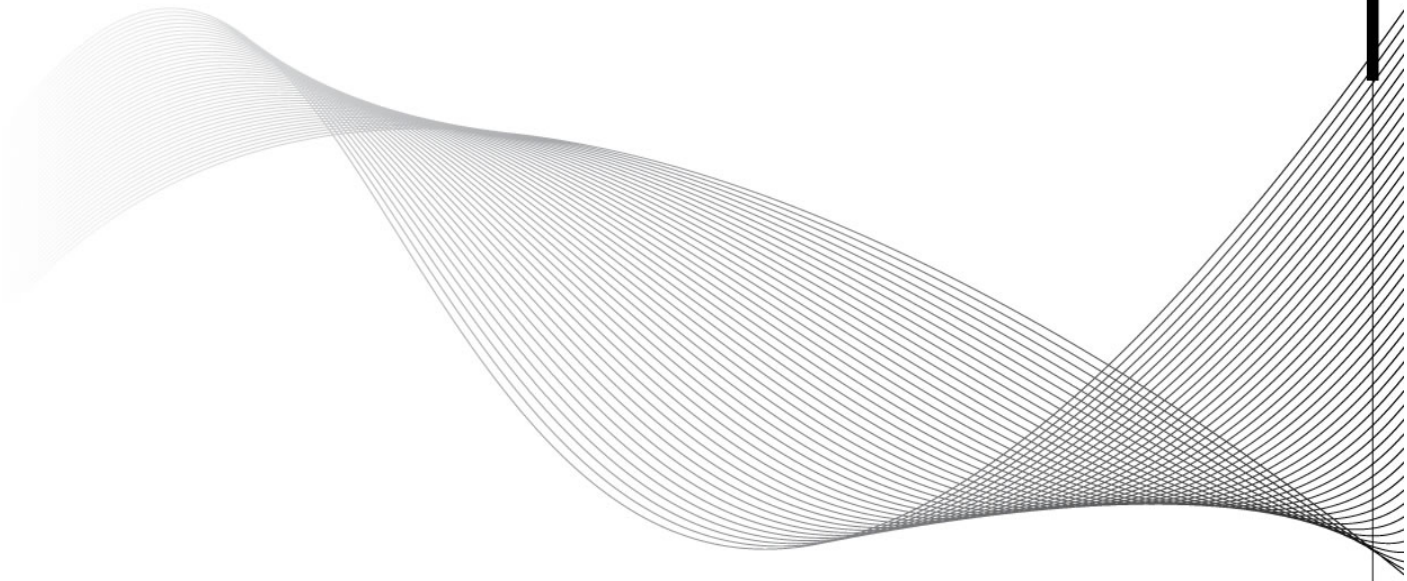

Recommendation from the Scientific Committee on Occupational Exposure Limits for Platinum and Platinum compounds

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8 hour TWA: not assigned
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Additional classification: not assigned
BLV: not assigned

This evaluation is based on the DECOS document Platinum and Platinum compounds (2008) which was prepared in co-operation with the Nordic Expert Group for Criteria Documentation of Health Risks for Chemicals (NEG).

Substance identification

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

Table 1 Chemical identification of platinum and relevant platinum salts.

chemical name *synonyms*	formula	molecular weight	CAS number	EINECS number	EEC number	RTECS number
platinum *platin, platinum metal, platinum black, platinum sponge, liquid bright platinum*	Pt	195.09	7440-06-4	231-116-1	not listed	TP2160000
platinum(II) oxide *platinum monoxide, platinous oxide*	PtO	211.08	12035-82-4	234-831-7	not listed	not listed
platinum(IV) oxide *platinum dioxide, platinic oxide*	PtO_2	227.08	1314-15-4	215-233-0	not listed	not listed
platinum(II) sulphide	PtS	227.15	12038-20-9	234-875-7	not listed	not listed
platinum(IV) sulphide	PtS_2	259.21	12038-21-0	234-876-2	not listed	not listed
platinum(II) chloride *platinous (di)chloride, platinum dichloride*	$PtCl_2$	265.99	10025-65-7	233-034-1	not listed	TP2275000
platinum(IV) chloride *platinum tetrachloride, tetrachloroplatinum*	$PtCl_4$	336.89	37773-49-2 (pentahydrate: 13454-96-1)	not listed (pentahydrate: 236-645-1)	not listed	TP2275550
platinum(IV) sulphate (tetrahydrate)	$Pt(SO_4)_2.4H_2O$	459.27	-	not listed	not listed	not listed
hexachloroplatinic(IV) acid *(chloro)platinic acid, (di)hydrogen hexachloroplatinate*	H_2PtCl_6	409.81	16941-12-1 (hexahydrate: 18497-13-7)	241-010-7 (hexahydrate: not listed)	078-009-00-4	TP1500000
ammonium tetrachloroplatinate(II) *ammonium chloroplatinite, diammonium tetrachloroplatinate, platinous ammonium chloride*	$(NH_4)_2PtCl_4$	372.97	13820-41-2	237-499-1	078-002-00-6	TP1840000
ammonium hexachloroplatinate(IV) *diammonium hexachloroplatinate, platinic ammonium chloride*	$(NH_4)_2PtCl_6$	443.87	16919-58-7	240-973-0	078-008-00-9	BP5425000
potassium tetrachloroplatinate(II) *potassium chloroplatinite, dipotassium tetrachloroplatinate, platinous potassium chloride*	K_2PtCl_4	415.09	10025-99-7	233-050-9	078-004-00-7	TP1850000
potassium hexachloroplatinate(IV) *dipotassium hexachloroplatinate platinic potassium chloride*	K_2PtCl_6	485.99	16921-30-5	240-979-3	078-007-00-3	TP1650000
sodium hexachloroplatinate(IV) *disodium hexachloroplatinate, sodium platinum chloride*	Na_2PtCl_6	453.77	16923-58-3	240-983-5	078-006-00-8	not listed
tetraammineplatinum dichloride *platinumtetraammine dichloride tetraamminedichloroplatinum(II) tetraammineplatinum(II) chloride*	$[Pt(NH_3)_4]Cl_2$	334.11	13933-32-9	not listed	not listed	not listed

Platinum (Pt) is a noble metal with atomic number 78. It belongs to group VIII of the periodic system, more precisely, the subgroup to which also nickel and palladium belong. The main oxidation states of platinum are +2 and +4; the first one is the most common (NAS, 1977). Platinum binds to a large number of inorganic and organic ligands and such compounds, for example cisplatin and carboplatin have medical use as chemotherapeutic agents (and are not covered in the present report) (Hägg, 1963; Parrot et al., 1969). The physical and chemical properties of platinum and its compounds covered in this report are listed in Table 2 (data from Lide, 1995).

Table 2 Physical and chemical properties of platinum and relevant platinum compounds.

chemical name	formula	molecular weight	melting point (°C)	density (kg/m³)	solubility in water
platinum [a]	Pt	195.09	1768	21.45 [b]	insoluble
platinum(II) oxide	PtO	211.08	325 [c]	14.1	insoluble
platinum(IV) oxide	PtO_2	227.08	450	11.8	insoluble
platinum(II) sulphide	PtS	227.15	-	10.25	insoluble
platinum(IV) sulphide	PtS_2	259.21	225-250 [c]	7.85	insoluble
platinum(II) chloride	$PtCl_2$	265.99	581 [c]	6.0	insoluble
platinum(IV) chloride	$PtCl_4$	336.89	327 [c]	4.30	slightly soluble
			- [d]	2.43 [d]	soluble [d]
platinum(IV) sulphate tetrahydrate	$Pt(SO_4)_2.4H_2O$	459.27	-	-	soluble
hexachloroplatinic(IV) acid	H_2PtCl_6	409.81	60 [e]	2.43 [e]	very soluble [e]
ammonium hetrachloroplatinate(II)	$(NH_4)_2PtCl_4$	372.97	- [c]	2.94	soluble
ammonium hexachloroplatinate(IV)	$(NH_4)_2PtCl_6$	443.87	380 [c]	3.07	slightly soluble
potassium tetrachloroplatinate(II)	K_2PtCl_4	415.09	500 [c]	3.38	soluble
potassium hexachloroplatinate(IV)	K_2PtCl_6	485.99	250 [c]	3.50	slightly soluble
sodium hexachloroplatinate(IV)	Na_2PtCl_6	453.77	250 [c]	3.5	very soluble [e]
tetraammineplatinum dichloride	$[Pt(NH_3)_4]Cl_2$	333.98	250 [f]	2.7	soluble

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

EU classification and labelling

The platinum salts covered in this report which have been classified and labelled in the European Union (Commission Directive 67/548/EEC) are listed in Table 3. Platinum itself and some of its salts have not been classified/labelled (see Table 1).

Table 3 Classification and labelling of relevant platinum salts.

substance	EINECS number	classification and risk phrases	safety phrases
hexachloroplatinic(IV) acid H_2PtCl_6	241-010-7	T; R25 C; R34 R42/43	1/2 – 22 – 26 – 36/37/39 – 45
ammonium tetrachloroplatinate(II) $(NH_4)_2PtCl_4$	237-499-1	T; R25 Xi; R38-41 R42/43	2 – 22 – 26 – 36/37/39 – 45
ammonium hexachloroplatinate(IV) $(NH_4)_2PtCl_6$	240-973-0	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 45
potassium tetrachloroplatinate(II) K_2PtCl_4	233-050-9	T; R25 Xi; R38-41 R42/43	2 – 22 – 26 – 36/37/39 – 45
potassium hexachloroplatinate(IV) K_2PtCl_6	240-979-3	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 45
sodium hexachloroplatinate(IV) Na_2PtCl_6	240-983-5	T; R25 Xi; R41 R42/43	1/2 – 22 – 26 – 36/37/39 – 45

T: Toxic; Xi: Irritant; C: Corrosive; R25: Toxic if swallowed; R34: causes burns; R41: Risk of serious damage to eyes; R42/43: May cause sensitisation by inhalation and skin contact;

1. Occurrence/use and occupational exposure

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

Platinum is obtained from mined ore and recycled metal. It is refined by treatment with aqua regia ($HCl:HNO_3$ 3:1) or HCl/Cl_2 yielding hexachloroplatinic(IV) acid, which is the general source of many other platinum compounds (see Part 2).

In 2005, ca. 62 tonnes of platinum were used in Europe, about 76% of which in the automotive industry (catalysts). Germany, UK, and France used about 4% and 2% in jewellery and in electronics, respectively, and Germany about 2% in dentistry. Worldwide, ca. 51% of the amount produced was used in the automotive industry, ca. 12% in jewellery, ca. 4% in electronics, and ca. 4% in chemical/petroleum refining; smaller amounts (ca. 1%) were used in dentistry and medicine as anti-cancer drugs such as cisplatin, which has been classified as a group 2A carcinogen by IARC (1987). In 2005, the world supply of platinum amounted to ca. 225 tonnes, an increase of roughly 50% compared with the period 1995-2000. Most of this supply originated from mine production (ca. 78%), the remainder form Russian exports (ca. 10%) and secondary sources (10%) such as scrap (recovery from auto catalysts). South Africa is by far the major mine producer accounting for ca. 90%, followed by Canada (4%), Zimbabwe (3%), and the USA (2%). For 2006, an increase of about 10% is expected (CPM Group, 2006). The production of platinum has generally followed its demand. Demands are expected to increase further due to the increasing demand for autocatalysts and the anticipated further development of fuel cells (UK Department for Transport).

Occupational exposure to platinum may occur during mining, refining and processing, manufacturing of platinum-containing products, and research on platinum catalysts. The very scarce data of platinum air levels in mines indicate very low concentrations: <0.4 µg/m^3 (Johnson et al., 1976). In refinery plants, levels of 0.02 µg up to 80 mg per m^3 were reported, the highest levels (5-80 mg/m^3) were noted in a poorly ventilated plant in China (Shi, 1987. In general, however, the available data indicate maximum levels of approximately 0.9-1.7 mg/m^3 (Bolm-Audorff et al., 1992; Fothergill et al., 1945; Hunter et al, 1945; Merget et al., 1988; Shi, 1987). In recycling plants, the levels varied between 0.4 and 240 µg/m3 (Hery et al., 1994); for other platinum-applying industries, air levels of 0.1-20 µg/m^3 have been published (Granlund, 1991; HSE, 1996; Schaller et al., 1992; Shima et al.,1984). The UK Health and Safety Executive (HSE), which reviewed the available data in 1996, reported that 96% of all occupational exposure data (measured as 8-hour time-weighted average) were below 2 µg/m^3. The majority of the data above 2 µg/m^3 occurred during the production and dispensing of soluble platinum salts (HSE, 1996).

2. Health significance

2.1 Toxicokinetics

2.1.1 Human data

A relatively large peroral uptake (at least 42%) of platinum from a hypothetical diet was found in humans (Vaughan and Florence, 1992).

Platinum levels in tissues of humans not occupationally exposed to platinum compounds varied greatly from <1 to ca. 1200 ng/g wet tissue (e.g. liver, kidney, lung, spleen, heart and muscle) weight. Remarkably also in fat, significant platinum levels were observed in some studies (Duffield et al., 1976; Johnson et al., 1976; Wester, 1965; Yoshinaga et al., 1990; Zeisler and Greenberg, 1988). Benes et al. (2000) reported a great variation in the platinum content in human tissues. In 70 autopsied individuals (54 males, 16 females; age: 18-76 years) from the North Bohemia territory of the Czech Republic, the platinum content in liver, kidney, and bone was found to be in the range of 2-3920; 2.5-750; and 10-230 µg/kg wet weight, respectively. No significant differences were seen between males and females.

Schierl et al. (1998; 1999) investigated the urinary excretion in humans. Thirty-four workers (32 men, 2 women) from a platinum refinery and catalyst production company were divided into four groups: (1) current high exposure (mainly K2PtCl4 and Pt(NO3)2), (2) former high exposure (stopped exposure 2-6 years ago because of hypersensitisation), (3) current low exposure (only occasionally exposed to lower levels), and (4) control group (no exposure). Sampling always included two spot urine samples, one at the end of a shift at the factory and a second one the next morning at home. For group 1, air platinum concentrations ranged from 0.2-3.4 µg/m3 (stationary) and from 0.8-7.5 µg/m3 (personal air sampling, PAS) with mean values of 1.1 and 2.5 µg/m3, respectively. For the control group, concentrations were <0.007 µg/m3. Urinary platinum excretion from workers after a shift (group 1) was found to be increased 1000 times up to 6270 ng/g creatinine. The urinary platinum excretion of the next morning was less increased (500 times; up to 2620 ng/g creatinine). Employees not exposed for several years (group 2) and free from symptoms still excreted 25 fold more platinum than the control group, indicating that there may be a long-lasting platinum pool in the body. Platinum excretion in occasionally exposed workers (group 3) was closer to the control group (increase: after a shift, 3-40 fold; at the next morning, 3-8 fold). Schierl et al. (1998; 1999) investigated the excretion kinetics of platinum in more detail by exposing two human volunteers by inhalation to concentrations of NH4)2PtCl6 of 0.15 (person A) and 1.7 µg/m3 (person B), respectively (amount of platinum measured on filters in breathing zone: person A: 60 ng and person B: 800 ng platinum, measured on filters in the breathing zone) for four hours. Platinum

excretion was measured in all urine sampled the next four days and in samples taken less frequently in the next four months. The excretion of platinum showed to be fast and dependent on exposure concentration. A steep increase (15 to 100 fold) in urinary platinum was found reaching its maximum nearly ten hours after inhalation: 23 ng/g creatinine in person A and 520 ng/g creatinine in person B (absolute levels of platinum excretion not given). Only in the case of high platinum exposure, the clearance was biphasic: for both persons a half-live of 50 h (95% confidence interval: 36-66 h) was calculated, while for person B a second half-life of 24 d (95% confidence interval: 18-33 d) was found (biphasic profile).

2.1.2. Animal Data

Experiments in which rats inhaled radiolabelled platinum and soluble and insoluble platinum compounds (5-8 mg/m3 for 48 minutes; particle size of soluble compounds: 1.0 µm) indicated little absorption. Most of the radioactivity was cleared from the lungs by mucociliary action, swallowed, and excreted via the faeces. The insoluble platinum compounds were longer retained in the lungs than the soluble ones. (Moore et al., 1975c; Artelt et al., 1999).

Automobile exhaust catalytic converters emit fine dispersed elemental platinum, Pt (0), in the nanometer range coated on larger aluminium oxide carrier particles. A pre-requisite for a potential systemic toxic effect of the emitted platinum is its bioavailability which was investigated using laboratory animals. To this end, a model substance was synthesised which consisted of aluminium oxide particles < or = 5 microns onto which platinum particles > or = 4 nm were deposited by a calcination process. These particles closely resemble those emitted from automobile exhaust converters. This model substance was applied to female Lewis rats in two doses by intratracheal instillation; the animals were killed after 1, 7, 28 and 90 days. In addition, the model substance was also applied during a 90-day inhalation study. After microwave digestion of the tissues, the platinum was determined in all organs and body fluids by inductively coupled plasma/mass spectrometry (ICP/MS). Platinum was found in the blood, urine and faeces and all important organs (liver, spleen, kidneys, adrenals, stomach, femur). Based on the platinum content determined in the body fluids and all organs (except the lung and the faeces) it was calculated that up to 16% of the platinum was retained in the lung 1 day after intratracheal instillation and up to 30% of the fine dispersed platinum deposited on an average during 90 days inhalation in the lung was bioavailable. Using size exclusion chromatography (SEC) in combination with ICP/MS, it was shown that > or = 90% of the bioavailable platinum was bound to high molecular weight compounds (approximately 80-800 kDa), most likely proteins.

Quantitative data on dermal absorption were lacking. In one experimental animal study, platinum was found in all internal organs, blood, and urine after dermal application of ammonium chloroplatinate (Roshchin et al, 1984), but in a sensitisation study with guinea pigs and rabbits, no platinum could be detected in urine, serum, or spleen following repeated dermal application of platinum sulphate (Taubler, 1977).

Gastrointestinal absorption appeared to be rather small, although soluble platinum chloride was better absorbed than platinum metal (no quantitative data). (Bogenrieder et al., 1993; Holbrook et al., 1975; Lown et al., 1980)

During the first week after intravenous administration of radiolabelled platinum salts to rats, radioactivity was found in all tissues analysed: the largest amount in the kidney, the lowest amount in the brain. The decrease in tissue content of platinum roughly paralleled the decline of blood concentration (Durbin, 1960; Moore et al., 1975a; Moore et al., 1975b).

Exposure to radiolabelled platinum metal or platinum oxide through inhalation (unknown particle size) led to immediate accumulation in the respiratory and gastrointestinal tracts. Next to these, kidney and bone were found to contain the highest concentration of radioactivity (Moore et al., 1975c).

Oral administration of water-soluble platinum salts resulted in much higher platinum concentrations in blood and tissues than administration of comparable doses of platinum metal. Particle size was found to influence the tissue concentrations of platinum, particularly in the kidneys, but details of the particle sizes were not reported. In general, the absorbed platinum (orally given as metal, II- or IV-chloride, or IV-sulphate) was distributed to virtually all organs and tissues; usually, the highest amounts were found in the kidneys, while low levels were found in adipose tissues and brain (Bader et al., 1991; Bader et al., 1992; Bogenrieder et al., 1993; Holbrook et al., 1975; Lown et al., 1980; Moore et al., 1975a; Moore et al., 1975b; Reichlmayr-Lais et al., 1992).

Fetal uptake after administration of different platinum salts to pregnant rats and mice has been shown to be very low. In a study with intravenously administered radiolabelled platinum(IV)chloride to pregnant rats, the fetuses contained 0.01% of the dose per gram whole fetal tissue and 0.05% of the dose per gram fetal liver (24 hours after dosing). Placental levels were much higher (0.9% of the dose per gram tissue) (Moore et al., 1975a).

After intravenous administration of radiolabelled platinum(IV)chloride to rats, the majority of the radioactivity was excreted into the urine and a lesser amount into the faeces. Thirty-five percent was excreted in the first three days, 86% after 28 days (Moore et al., 1975b).

After inhalation exposure of rats for 48 minutes to labelled particulates (5-8 mg/m3) of platinum(IV)chloride, platinum(IV)sulphate, platinum(IV)oxide or platinum metal , most of the radiolabel was excreted with the faeces during the first days; only small amounts were present in the urine (ratio faeces:urine was not reported). Clearance appeared to be biphasic: an initial rapid phase was followed by a slower second phase. The whole body retention of radioactivity as a percentage of the initial body burden 24 hours after exposure was 20-40%, while after ten days more than 90% had been excreted (Moore et al., 1975c).

Platinum(IV)chloride orally given to rats was mainly excreted via the faeces, suggesting that the majority had passed the gastrointestinal tract unabsorbed.(Moore et al., 1975a; Moore et al., 1975b).

Following intravenous injection of 1064 µg K2PtCl4 (total Pt: 500 µg/rat) into female Lewis rats, ca. 50 and 41% of the total platinum were excreted within ten days via the kidneys and urine and via the bile and faeces, respectively. Excretion via the faeces occurred somewhat faster than via the urine (roughly 60 and 70% within one and two days, respectively, vs. roughly 40 and 50%, respectively) (Artelt et al., 1999).

2.1.3. Biological Monitoring

Background levels of platinum in blood and urine are suggested to be in the order of some nanogrammes per L (blood or plasma: <0.8-7 ng/L; urine: 0.5-15 ng/L), with a significant correlation between levels in blood, serum, and urine (Ensslin et al., 1994; Messerschmidt et al., 1992; Schaller et al., 1992). Other reports indicate 100-200 times higher values (blood about 500-600 ng/L; urine: about 250 ng/L), but doubts have arisen as to the reliability of these analyses (Johnson et al., 1975; Nygren et al., 1990; Nygren et al ., 1991; Vaughan and Florence, 1992).

A study of 40 occupationally exposed people showed mean platinum blood and serum levels of 39 and 39 ng/L, respectively, in the production section and of 125 and 75 ng/L, respectively, in the mechanical treatment section. Urine levels were 1260, 330, and 430 ng/L in the people of the production, recycling, and mechanical treatment section, respectively. Data concerning exposure time were not reported. There was a significant correlation between levels in blood, serum, and urine, but not with the median concentrations in air, which were reported to be 3.1, 3.8, and 1.8 µg/m3 in the production, recycling, and mechanical treatment section, respectively (Schaller et al., 1992).

Petrucci et al. (2005) evaluated occupational exposure in an industrial plant in Italy engaged in the production, recovery, and recycling of catalytic converters for the automotive traction and chemical industries and the most reliable biomarker for this

exposure. The highest concentrations of platinum were found in the coating department with mean levels of 2.70 µg/m3 (range: 0.97-4.83 µg/m3) in personal air samples. The mean percentage of soluble platinum in these samples was ca. 30%. The corresponding mean concentrations in blood, urine and hair were 0.38, 1.86 and 2.26 µg/kg, respectively. Workers from departments with lower exposure levels had correspondingly lower platinum levels in urine, blood, and hair. Employees from departments with no direct exposure still had blood and urine levels that were about 20 times higher than those of unexposed controls living in a rural area (i.e., 0.01 and 0.005 µg/L, respectively). Petrucci et al. (2005) concluded that the differences in exposure as measured by personal air sampling were best reflected by the platinum levels found in the urine.

Other studies also demonstrated that platinum levels in blood and, especially, urine are good indicators of exposure to platinum. Farago et al. (1998) reported mean concentrations of platinum of 246 ng/L and of 470 ng/g creatinine in whole blood and urine, respectively, in seven platinum refinery workers, compared to levels of 145 ng/L and 58 ng/g creatinine and of 129 ng /L and 113 ng/g creatinine in ten motorway maintenance workers and five university staff people, respectively. There was a significant correlation between the blood and urine levels. Schierl et al. (1998; 1999) reported a mean urinary platinum concentration of 1994 ng/g creatinine (range: 170–6270 ng/g; 50 urine samples in total) in 15 'highly' occupationally exposed workers (mean exposure levels by personal air sampling: 2.5 µg/m3; range: 0.8-7.5 µg/m3). This was about 500 times the control value found in 12 unexposed persons (4 ng/g creatinine; range: 1-12 ng/g; 24 samples).

Further, Schierl et al. (1998; 1999) found increased urinary platinum concentrations in four persons who stopped working in platinum industry two to six years before (forced by platinum allergy) (120 ng/g creatinine; range: 10–170 ng/g; 10 samples). These data suggest that platinum accumulates in the body following occupational exposure and is only released very slowly.

2.2 Acute toxicity

2.2.1 Human data

Acute poisoning was reported for a 7-month-old child who died five hours after accidental administration of 8 g of potassium tetrachloroplatinate(II) (Hardman et al., 1986). A 31-year-old man who ingested 600 mg of potassium tetrachloroplatinate(II), corresponding to around 8 mg/kg bw or 4 mg Pt/kg bw, suffered from vomiting, diarrhoea, leg cramps, renal failure, gastroenteritis, fever, mild hepatitis, mild metabolic acidosis, eosinophilia and

leukocytosis. The initial serum platinum concentration was 245 µg/dl. All symptoms and signs of toxicity disappeared within six days (Woolf and Ebert, 1991).

2.2.2 Animal data

Within a given class of platinum compounds the acute toxicity follows the water solubility to some degree and generally the insoluble compounds are less toxic than the soluble ones (Holbrook et al., 1975; Holbrook, 1976; IPCS, 1991; NAS, 1977). Some soluble platinum salts (ammonium tetrachloroplatinate(II), ammonium hexachloroplatinate (IV), potassium tetrachloroplatinate(II), sodium hexachloroplatinate(IV)) are very toxic at peroral administration with LD50 values for rats of 25-210 mg/kg bw (around 10-110 mg Pt/kg bw), but many other platinum compounds are moderately or only slightly toxic. LD50 values in rat for platinum(IV)oxid and tetraammineplatinum(II) chloride were >3.4 g/kg bw (>2.9 g Pt/kg bw) and >15 g/kg bw (8.8 g Pt/kg bw), respectively, at peroral administration (Holbrook et al., 1975; Holbrook, 1976; IPCS, 1991; Ward et al., 1976).

Clinical signs of acute toxicity of ammonium tetrachloroplatinate(II) include diarrhoea, clonic convulsions, laboured respiration, and cyanosis (IPCS, 1991).

Hexachloroplatinic acid (40-50 mg/kg intraperitoneally) was highly nephrotoxic (severe tubular necrosis) in rats. Severe histopathological lesions were also observed in thymus (Ward et al., 1976). Platinum(IV)sulphate administered to mice at the LD25 level (213 mg Pt/kg intragastrically) affected their behaviour (general activity) (Lown et al., 1980). Remarkably, pre-treatment of rats with a single lower dose of platinum(IV)chloride 48 hours before a higher generally lethal dose of this salt caused markedly increased survival. (Holbrook et al., 1976).

2.3 Irritation

2.3.1 Human data

Occupational inhalation exposure to platinum salts (particularly the soluble ones) is a well-known cause of respiratory allergic manifestations and skin reactions (Boggs, 1985; Hostynek et al., 1993; Pepys and Hutchcroft, 1975; Rosner and Merget, 1990). The symptoms include lachrymation, irritation of the upper respiratory tract, rhinitis, coughing and asthma as well as angioedema and urticarial and eczematous skin lesions (Cleare et al., 1976; Hunter et al., 1945; Jordi, 1951; Marshall, 1952; Merget et al., 1988; Merget et al., 1991; Parrot et al., 1969; Roberts, 1951). Still, some of the reported symptoms may have been due to non-immunologic mechanisms, although in man the platinum salt-induced reactions of the respiratory tract and the skin generally is considered to be of immunologic origin (Levene and Calnan, 1971; Merget et al., 1991; Murdoch and Pepys, 1984; Parish,

1970; Pepys et al., 1979a; Schuppe et al., 1993; White and Cordasco, 1988). True allergic contact dermatitis from exposure to platinum compounds, however, is rare and the dermatitis seen sometimes may be of a primary irritant nature (Boggs, 1985; Fisher, 1986; Hughes, 1980; Jacobs, 1987; Linnett, 1987; Sheard 1955).

The EU classification and labelling indicate that soluble platinum salts are irritants and that there is risk of serious damage to the eyes (see table 3, p. 3 in this document).

2.3.2 Animal data

Animal data (table 6) indicate that soluble platinum compounds are slightly to irritating to the skin, whereas insoluble compounds are not. Further, the soluble compounds are irritating or even severely irritating or corrosive to the eye. No data were found for insoluble compounds (HSE, 1985; IPCS, 1991).

In Table 6, data on skin and eye irritation of several platinum compounds are summarised.

Table 6 Skin and eye irritation by platinum compounds [a] data from IPCS, 1991).

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

*NEG25

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

Platinum salts may induce bronchoconstriction, anaphylactic shock and elevated plasma histamine levels in animals at the first contact and without any previous exposure to platinum salts, thus through pharmacologic or irritant mechanisms (Biagini et al., 1983; Parrot et al., 1969; Saindelle and Ruff, 1969).

Increased pulmonary reactivity, expressed as significantly increased pulmonary flow resistance (RL) and decreased forced expiratory volume (FEV0.5/FVC), was found in male cynomolgus monkeys challenged with Na2PtCl6(IV) aerosols (up to 62.5 mg/mL solutions;) two weeks after a period of repeated inhalation exposure to about 216 µg/m3 of the platinum salt (4 hours/day, biweekly for 12 weeks, particle size: MMAD 1.61 µm), compared to a challenged, but previously unexposed control group. Increased bronchial reactivity (compared to the control group) was not seen at an exposure level around 1940 µg/m3. However, marked effects on the pulmonary function were found in all exposed and control animals challenged with the platinum salt., and these results indicate a pharmacologic or irritant-mediated bronchoconstriction mechanism for acute exposure to this compound. With the exposure regimens used, no effect on post-exposure baseline pulmonary function was found in exposed animals when challenged with saline. When compared on the basis of monkey-to-human minute volume ratio, a concentration of 200 µg/m3 (4 hours/day, biweekly for 12 weeks) results in an equivalent exposure of three to four times of that to which a worker would be exposed in one week at an air level of 2 µg/m3. (Biagini et al., 1983)

2.4 Sensitisation

The most significant health effect from exposure to soluble platinum compounds is sensitisation. Soluble platinum salts induce allergic reactions in which both the respiratory tract and the skin are involved. These reactions are caused by a humoral immune response, as was seen in exposed workers by increased levels of IgE, and in mice by an increased internalisation in Langerhans cells, lymph node cell proliferation and differentiation, and Th2-type cytokine production induced by soluble platinum salts such as sodium and ammonium tetra- and hexachloroplatinate. Complexes where there are no halogen ligands coordinated to platinum (such as e.g., tetraammineplatinum dichloride, and neutral complexes (such as cisplatin) failed to induce such effects.

Obviously, hexachloroplatinic acid and the tetra- and hexachloroplatinate salts are the compounds mainly responsible for platinum-salt allergy: these compounds have apparently the structural characteristics required to trigger sensitisation. All results together appear to indicate a dose-response relationship between the level of exposure and the extent of development of sensitisation. Sensitisation was shown to develop already at occupational exposure to airborne soluble platinum-salt levels of approximately 50-100

ng/m3 (expressed as Pt) , but not at levels <10 ng/m3 (Merget, 2000; Merget et al. 2000; Merget et al., 2001). No sensitisation was seen in workers exposed to tetraamineplatinum dichloride at levels up to 2000 ng/m3 (and occasionally >10,000 ng/m3) (Linnett and Hughes, 1999; Steinfort et al., 2008).

2.4.1 Human data

Platinum compounds mainly responsible for sensitisation are hexachloroplatinic(IV)acid and the chloroplatinate salts (Boggs, 1985; Freedman and Krupey, 1968; Hunter et al., 1945; Marshall, 1952; Parrot et al., 1969; Pepys and Hutchcroft, 1975; Pepys et al., 1972; Rosner and Merget, 1990). Clinical symptoms upon exposure to soluble platinum salts include lachrymation, irritation of the upper respiratory tract, rhinitis, asthma and coughing, as well as angioedema, urticarial and eczematous skin lesions and the symptoms tend to get worse upon continued exposure (Cleare et al., 1976; Hunter et al., 1945; Jordi, 1951; Marshall, 1952; Merget et al., 1988; Merget et al., 1991; Merget et al., 1994; Parrot et al., 1969; Roberts, 1951). However, the presence of both type I (immediate) and type IV (delayed) hypersensitivity has been described in sensitised workers exposed to "platinum dichloride" (Nakayama et al., 1997). Patch tests and a nasal test (0.5% PtCl2) were made. All 12 patients tested showed normal values of serum IgE. Metallic platinum is not associated with hypersensitivity, although a case of dermatitis due to a platinum ring (Sheard, 1955) and a case of contact stomatitis due to platinum in a dental alloy (Koch and Baum, 1996) has been reported.

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 (Dally et al., 1980; Hughes, 1980; Merget et al.,1988; Merget et al., 1991; Parkes, 1982; Parrot et al., 1969; Pepys et al., 1979a). An immunological reaction with platinum salts is often established in man by skin prick testing, but sometimes pulmonary reactions (expressed in bronchial provocation tests or as work-related symptoms) precede a positive response in skin test (Biagini et al., 1985a; Biagini et al., 1985b; Bolm-Audorff et al., 1992; Brooks et al., 1990; Cleare et al., 1976; Cromwell et al., 1979; Dally et al., 1980; Hughes, 1980; Merget et al., 1988; Merget et al., 1991; Murdoch et al., 1986; O'Hollaren, 1992; Pepys et al., 1972; Pickering, 1972; Venables et al., 1989; White and Cordasco, 1988). The presence of platinum salt-specific IgE antibodies in serum and unusually high levels of total serum IgE has been seen in exposed workers (Biagini et al., 1985a; Bolm-Audorff et al., 1992; Brooks et al., 1990; Cromwell et al., 1979; Merget et al., 1988; Murdoch et al., 1986; Murdoch et al., 1987; Pepys et al., 1979a; Pepys et al., 1979b; White and Cordasco, 1988; Zachgo et al., 1985).

Atopic as well as non-atopic workers may be affected (Brooks et al., 1990; Merget et al., 1988; O'Hollaren, 1992; Venables et al., 1989), and smoking appears to predispose individuals to the development of platinum salt-induced sensitisation after occupational exposure. (Baker et al., 1990; Brooks et al., 1990; Linnett, 1987; Venables et al., 1989). It has also been proposed that concurrent exposure to irritants (like chlorine, ammonia, or ozone) potentiates the effects of platinum-salt exposure in a way similar to tobacco smoke (Baker et al., 1990; Newman Taylor, 1994).

Newman Taylor et al. (1999) investigated a group of 101 employees of a platinum refinery, comparing 44 of them with a positive skin prick test to ammoniumhexachloroplatinate to 57 non-sensitised matching referents. They showed that the human leukocyte-associated antigen (HLA) phenotype was a significant determinant of sensitisation to ammonium hexachloroplatinate.

Raulf-Heimsoth et al. (2000; 2001) determined the T-cell receptor (TCR) expression, additional cell surface molecules, proliferation of peripheral blood mononuclear cells (PBMC), and cytokine production in 17 platinum salt-sensitised workers with workplace-related asthma and 15 asymptomatic non-exposed subjects. All sensitised workers showed a positive immediate-type skin prick test response to Na_2PtCl_6, and the IgE concentration was in the range of 17-657 kU/L (median: 110 kU/L).

The prevalence of respiratory and/or cutaneous symptoms among e.g. refinery workers exposed to platinum salts has been very high, frequently over 50% (Baker et al., 1990; Biagini et al., 1985a; Brooks et al., 1990; Hunter et al., 1945; Massmann and Opitz, 1954; Parrot et al., 1969; Roberts, 1951; Sauerwald, 1961; Venables et al., 1989). 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 and positive skin prick test results were seen also in areas where the mean air_concentration probably was below 2.0 µg/m3 (Bolm-Audorff et al., 1992; Merget et al., 1988; Merget et al., 1991). Santucci et al. (2000) reported positive prick test reactions in 22 out of 153 (14%) occupationally exposed workers, whereas the platinum salts tested never caused positive reactions in not occupationally exposed patients with dermatitis and/or urticaria.

Linnett and Hughes (1999) presented a retrospective analysis of the results of 20 years of medical surveillance at a UK platinum company of all new employees who started work between 1 January 1976 and 31 December 1995 and who were followed up until 31 December 1995. They worked in one of 3 operations on the same site: the platinum-group metals refinery with exclusive exposure to chloroplatinates ('PGM refinery'; n=406), the autocatalyst production with exclusive exposure to tetraammineplatinum dichloride

('Autocat'; n=100), and the tetraammineplatinum dichloride production with mixed exposure ('TPC lab'; n=41). All subjects were medically examined before employment and satisfied standards for work with soluble platinum compounds. Atopic subjects, identified by history or skin prick test to common aeroallergens, were not employed in production or technical positions. Smoking habit was recorded before employment. The medical surveillance routine included enquiry about symptoms and skin prick tests every three months with three different chloroplatinates, and spirometry every six months. Criteria for diagnosis of allergy were set. The results of the analyses showed a significant difference in the incidence of allergy in these operations. In subgroups consisting of chemical process operators being exposed to platinum compounds for at least 50% of their work (n=270, 40, and 31, respectively), the cumulative chance of being sensitised after five years of exposure was estimated to be 51% for chloroplatinate exposure, 0% for tetraammineplatinum dichloride exposure, and 33% for mixed exposure. The differences in sensitisation rates could neither be explained by age, sex, and atopy, nor by the higher number of smokers in the workers exposed to chloroplatinates, despite the markedly higher risk of sensitisation in smokers.

Merget and co-workers (2000; 2001; Merget, 2000) showed, in a five-year prospective cohort study, a clear dose-response relationship between airborne soluble platinum concentrations, platinum concentrations in sera of exposed workers, and newly occurring sensitisations. The study was performed in the period 1989-1995, and included a total of 275 employees of a catalyst-production plant in Germany, 115 of them working directly in the production lines ('high exposure'), 112 working regularly or irregularly within the catalyst department but not in the production lines ('low exposure'), and 48 who never entered the catalyst building ('no exposure'). Fifty-three per cent of the study population was already present when the study started. The study population consisted of subjects who had undergone at least 2 examinations and a negative response in the skin prick test against platinum at the initial survey.

The results demonstrated that in a population of 160 workers, no new cases of sensitisation occurred during five-year exposure to airborne soluble platinum concentrations in the 'no' and 'low exposure' areas. The maximum concentrations of soluble platinum measured in the 'low-exposure' area were 8.6 and 1.5 ng/m^3 in 1992 and 1993, respectively.

In the 'high exposure' area, 14 new cases of sensitisation occurred in 115 exposed workers (11%). In this area, the maximum concentrations of soluble platinum measured were roughly 700 (1992) and 155 (1993) ng/m^3. Personal sampling (of inhalable dust) in this area revealed a median value of 177 ng/m3 with a highest value of 3700 ng/m^3; 3 samples out of 22 exceeded 2000 ng/m^3 (8 h sampling time). Smoking cigarettes was positively associated with the occurrence of new symptoms.

Exposures below the occupational threshold limit value (generally 2000 ng Pt/m3) may still result in sensitisation. Even exposure to soluble platinum salts at levels between 10 and 100 ng Pt/m^3 may lead to sensitisation. Because other sources indicate that sensitisation to platinum salts rarely occurs after 5 years of exposure (Schuppe et al., 1997a) the results of the prospective cohort study of Merget et al., (200, 2001; Merget, 2000) suggest that at exposure to levels below 10 ng/m^3 sensitisation is not to be expected.

SCOEL noted, however, that this study was not conducted with the aim to find a NOAEL. SCOEL further noted the lack of quantification of peak exposures, that high exposures may have occurred in the past which could have contributed to the sensitisation cases, that the exposure estimates were not based on the sampling and highly variable exposures, all of which may lead to unreliable exposure estimates.

2.4.2 Animal data

US EPA investigated the potential for skin sensitisation of $PtCl_4$ and $Pt(SO_4)_2$ in rats, mice, and guinea pigs. No allergic induction was shown when 50-350 µg/mL $Pt(SO_4)_2$ was repeatedly injected subcutaneously or intravenously, or when $Pt(SO_4)_2$ paste (0.1-0.25 g per application) was repeatedly applied to the skin. Also $PtCl_4$ repeatedly given to guinea pigs (1.5-4.5 mg/mL subcutaneously) was negative when tested for skin reactions 14 days after the last injection (Taubler, 1977).
$(NH_4)_2PtCl_4$ was tested in the guinea pig maximisation test with Dunkin-Hartley guinea pigs and the local lymph node assay in CBA/Ca mice to predict the skin sensitisation potential. The substance was classified as an extreme sensitiser in the maximisation test (intradermal induction injections: 0.05%; induction patch: 5%; challenge patch: 1%), and was found positive by producing a proliferative response in the lymph node assay (topical applications of 2.5, 5 or 10%) (Basketter and Scholes, 1992).

With respect to mechanisms of action of sensitisation and immune response, a number of studies with soluble platinum compounds have been conducted in mice (Mandervelt et al., 1997; Schuppe et al., 1997a; 1997b; Dearman et al., 1998; Chen et al., 2002). In summary, studying the immune response in mice using the soluble platinum salts Na_2PtCl_4(II), Na_2PtCl_6(IV), $(NH_4)_2PtCl_4$(II), $(NH_4)_2PtCl_6$(IV) and/or K_2PtCl_4(II), the following effects were found (see also Table 7):

- stimulation of receptor-mediated endocytosis in Langerhans cells (essential for antigen presentation to pre-T helper cells);
- stimulation of cell proliferation in lymph nodes with the majority of proliferating cells being CD4+ T-cells (T helper cells; essential for cytokine production);

- stimulation of Th2-type cytokine production (IL-4 and IL-10) in lymph node cells (essential for B cell stimulation; stimulation of the humoral immune response);
- inhibition of Th1-type cytokine production (IFN-γ) in lymph node cells (essential for macrophage stimulation; suppression of the cell mediated immune response);
- stimulation of anti-nuclear autoantibodies.

The results confirm the sensitisation potential of soluble platinum salts like the tetra- and hexachloroplatinates, i.e., salts with a halogen ligand coordinated to platinum. Tetraamineplatinum(II) chloride, where there is no halogen ligand coordinated to platinum but the halogen is present as an ion, failed to induce sensitisation.

Effects on the mouse immune system are summarised in Table 7.

Table 7 Effects on immunology measured in the mouse.

compound	species	assay	sensitisation	Effects	reference
sodium hexachloro-platinate(IV) Na_2PtCl_6	mouse	LLNA [a], PLN [b], ALN [c] assay	ears (3-4x ec [f]), footpad (1x sc [f]), flank (2x ec) + ears (3x ec)	increased proliferation; increased percentage of CD4+ T-cells, enhanced IL-4 and IL-6 (IL-10?) levels, decreased IFN-γ,	Mandervelt et al., 1997; Schuppe et al., 1997a; 1997b
	mouse	endocytosis assay (Langerhans cells)		increased endocytosis	Schuppe et al., 1997a;
	mouse	MEST [d]	ear (4-8x ec + challenge(s))	induction of contact hypersensitivity?, swelling of the challenged ear (dermal oedema, inflammatory cells); irritant reaction of the contra-lateral ear used for sensitisation	Schuppe et al., 1997b;
	mouse	Assay on ANA [e]	24x sc	ANA^5 production	Chen et al., 2002
sodium tetrachloro-platinate(II) Na_2PtCl_4	mouse	PLN, ALN assay	footpad (1x sc), flank (2x ec) + ears (3x ec)	increased proliferation; increased percentage of CD4+ T-cells; enhanced IL-4 and IL-6 (IL-10?) levels	Schuppe et al., 1997a;
	mouse	endocytosis assay (Langerhans		increased endocytosis	Schuppe et al., 1997a;

		cells)			
potassium tetrachloro-platinate (II) K_2PtCl_6	mouse	PLN assay	footpad (1x sc)	increased proliferation; Increased percentage of CD4+ T-cells	Schuppe et al., 1997a;
	mouse	endocytosis assay (Langerhans cells)		increased endocytosis	Schuppe et al., 1997a;
tetraammineplatinum dichloride $Pt(NH_3)_4Cl_2$	mouse	PLN assay	footpad (1x sc)	no PLN reaction	Schuppe et al., 1997a;
	mouse	endocytosis assay (Langerhans cells)		no effect	Schuppe et al., 1997a;

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

2.5 Repeated dose toxicity

2.5.2 Animal data

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.

There was a decrease in weight gain (and water consumption) in rats given drinking water containing 235 or 470 mg/L (ppm) potassium tetrachloroplatinate (II) for 23 days (Moore et al., 1975b). Transient decrease in weight gain and increased relative kidney weight was seen in male rat at administration of about 40 mg platinum/kg bw/day, when platinum(IV)chloride was added to the drinking water (550 ppm) for four weeks, whereas similar exposure to 10 mg Pt/kg bw/day did not affect body or kidney weights (Holbrook et al., 1975). The erythrocyte count and hematocrit were reduced by about 13% and a significant increase of creatinine content in plasma, but no influence on body weight gain, was shown in another study in male rat, when platinum(IV)chloride was added in the diet

(50 mg Pt/kg diet) for 4 weeks at doses corresponding to around 5 mg Pt/kg bw/day (Reichlmayr-Lais et al., 1992). In a similar experiment with platinum(II)chloride, neither hematological parameters, plasma creatinine nor body weight gain were affected (Reichlmayr-Lais et al., 1992). No treatment-related changes in haematological values, growth rate or kidney weights were noticed when female rats were fed a diet containing platinum(IV)chloride in a concentration of up to 100 mg Pt/kg diet, four weeks before and during gestation (Bogenrieder et al., 1992).

Data on inhalation exposure are very scarce and unreliable. No overt ill effects and no significant differences in body weights were observed for male Cynomolgus monkeys exposed by inhalation to 177 µg/m3 ammonium hexachloroplatinate(IV) for 12 weeks (6 hours/day, 5 days/ week; MMAD 1 µm). However, the study was designed to detect differences in immunologic parameters and effects in the airways (Biagini et al., 1986).

2.6 Genotoxicity

For the only insoluble platinum compound tested, viz., platinum(II)chloride, *in vitro* tests for mutations (mouse lymphoma L5178Y cells) (Sandhu, 1979) and DNA damage in bacteria (*E. coli*: SOS chromotest) (Gebel et al., 1997) and mammalian cells (human lymphocytes: comet assay) (Migliore et al., 2002) were negative. Both positive (Migliore et al., 2002) and negative– (Gebel et al., 1997) results were reported in micronucleus tests in human lymphocytes. The induction of micronuclei was due both to clastogenic and aneuploidogenic mechanisms (Migliore et al., 2002). Numerous soluble platinum compounds have been tested for their mutagenic activity *in vitro* in bacterial and mammalian cell systems, mostly without metabolic activation, and in fruit flies. Many of the compounds were positive. Some of the compounds were tested for other end points in other systems (e.g. *E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes/leukocytes: micronucleus test and comet assay), inducing both positive and negative results (Bünger et al., 1996; 1997; Gebel et al., 1997; (Migliore et al., 2002; Casto et al., 1979; HSE,1996; Hsie, 1981; Johnson et al., 1980; Kanematsu et al., 1980; 1990; Lecointe et al., 1977; Sandhu,1979; Smith, 1984; Sora and Magni, 1988; Taylor et al., 1978; 1979a; 1979b; 1985; Uno and Morita, 1993; Woodruff et al., 1980).

The anti-neoplastic agent cisplatin binds to DNA and is mutagenic *in vitro* and *in vivo*. Platinum compounds with a similar structure and configuration, particularly complexes with the same square-planar configuration of cis-PtN_2X_2, generally also have mutagenic activity (Uno and Morita, 1993). The results of genotoxicity studies are summarised in Table 8.

Table 8 Genotoxic activity of some platinum salts in *different* test systems (NEG data and additional data).

Compound	test system	metabolic activation	result	reference
platinum(II) chloride	*E. coli* PQ37; SOS chromotest	-	-	Gebel et al., 1997
	mouse lymphoma L5178Y cells; mutation assay	-	-	Sandhu,1979;
	human lymphocytes; micronucleus test	-	-	Gebel et al., 1997
	human lymphocytes; micronucleus test + FISH [a]	-	+	Migliore et al., 2002
	human leukocytes; comet assay	-	-	Migliore et al., 2002
platinum(IV) chloride	*S. typhimurium* TA98; mutation assay	-	+	Kanematsu et al., 1980
	S. typhimurium TA100, TA1535, TA1537, TA1538; mutation assay	-	-	Kanematsu et al., 1980, Uno and Morita, 1993
	E. coli B/r WP2 *try*, WP2 *hcr try*; mutation assay	-	-	Kanematsu et al., 1980
	E. coli PQ37 ; SOS chromotest	-	+	Gebel et al., 1997
	B. subtilis H17 M45 ; rec-assay	-	+	Kanematsu et al., 1980
	D. melanogaster; sex-linked recessive lethal mutation assay		+	Woodruff et al., 1980
	Chinese hamster lung V79 cells; mutation assay	-	+	Kanematsu et al., 1990
	Chinese hamster ovary S cells; mutation assay	-	+	Taylor et al., 1979b
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	Taylor et al., 1979b
	mouse lymphoma L5178Y cells ; mutation assay	-	+	Sandhu,1979;
	human lymphocytes; micronucleus test	-	+	Gebel et al., 1997
	human lymphocytes; micronucleus test + FISH [a]	-	+	Migliore et al., 2002
	human leukocytes; comet assay	-	+	Migliore et al., 2002
	Syrian hamster embryo cells; cell transformation assay	-	+	Casto et al., 1979
platinum(IV) sulphate	Chinese hamster ovary S cells; mutation assay	-	+	Smith et al., 1984; Taylor et al. 1979a
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	Taylor et al., 1985
hexachloroplatinic (IV) acid	*S. typhimurium* TA98; mutation assay	+	+	Uno and Morita, 1993
	S. typhimurium TA 100; mutation assay	+	-	Uno and Morita, 1993
	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 ; mutation assay	-	-	Kanematsu et al., 1980
	E. coli B/r WP2 *try*, WP2 *hcr try*; mutation assay	-	-	Kanematsu et al., 1980
	B. subtilis H17 M45 ; rec-assay	-	+	Kanematsu et al., 1980
potassium tetra-chloroplatinate(II)	*S. typhimurium TA98, TA100;* mutation assay	-/+	+/+	Lecointe et al., 1977; + Uno and Morita, 1993
	E. coli PQ37; SOS chromotest	-	+	Gebel et al., 1997
	S. cerevisiae ; assay for aneuploidy	-	+	Sora et al., 1988
	D. melanogaster; sex-linked recessive lethal mutation assay		-	HSE, 1996
	Chinese hamster ovary S cells; mutation assay	-	-	Taylor et al., 1979a
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	Taylor et al., 1978
	Chinese hamster ovary K1-BH4 cells; mutation assay	-	(+) b	Hsie, 1981; Johnson et al., 1980
	human blood lymphocytes; micronucleus test	-	+	Gebel et al., 1997
potassium hexa-chloroplatinate(IV)	*S. typhimurium TA97a, TA98, TA100, TA102 ; mutation assay*	-/+	+/+	Bünger et al., 1996 + 1997
	E. coli PQ37 ; SOS chromotest	-	-	Gebel et al., 1997
	Chinese hamster ovary S cells; mutation assay	-	+	Smith et al., 1984; Taylor

				et al., 1979a
	Chinese hamster ovary AUXB1 cells; mutation assay	-	+	Taylor et al., 1978
	human lymphocytes; micronucleus test	-	-	Gebel et al., 1997
ammonium hexa-chloroplatinate(IV)	*S. typhimurium TA97a, TA98, TA100, TA102 ; mutation assay*	-/+	+/+	Bünger et al., 1996; 1997
	S. typhimurium TA98, mutation assay	-	+	Kanematsu et al., 1980
	S. typhimurium TA1537,TA1538, mutation assay	-	-	Kanematsu et al., 1980
	E. coli B/r WP2 try; mutation assay	-	-	Kanematsu et al., 1980
	E. coli WP2 hcr try; mutation assay	-	+	Kanematsu et al., 1980
	B. subtililis H17 M45 ; rec-assay	-	+	Kanematsu et al., 1980
ammonium tetra-chloroplatinate(II)	*S. typhimurium TA97a, TA98, TA100, TA102; mutation assay*	-/+	+/+	Bünger et al., 1996; 1997
	human lymphocytes; micronucleus test + FISH a	-	+	Migliore et al., 2002
	human leukocytes; comet assay	-	-	Migliore et al., 2002
tetraammineplatinum dichloride	*S. typhimurium TA98, TA100 ; mutation assay*	-/+	-/-	Uno and Morita, 1993
	S. typhimurium TA100; mutation assay	not given	+	Lecointe et al., 1977
	S. typhimurium TA98, TA100, TA1535, TA1538; mutation assay	not given	-	HSE, 1996
	S. typhimurium TA1537; mutation assay	-/+	+/+	HSE, 1996
	Chinese hamster ovary K1-BH4 cells; mutation assay	-	-	Hsie, 1981[b]; Johnson et al., 1980
	D. melanogaster; sex-linked recessive lethal mutation assay		-	HSE, 1996

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

[b] 'Marginally' positive.

2.7 Carcinogenicity

Except for cisplatin and some related compounds (which are known carcinogens), studies on the (potential) carcinogenicity of platinum metal and platinum compounds were not located.

2.8 Reproductive toxicity

Data on reproductive and developmental toxicity are very limited. No effects were seen in rat fetuses (weight, resorptions, malformations) following daily administration of doses of platinum metal or platinum(IV) chloride of 0.1-100 mg Pt/kg diet, for 4 weeks before pregnancy to gestational day 20 (Bogenrieder et al., 1992). Further, no effects on weight or haematology were seen in the offspring (Kirchgessner and Reichlmayr-Lais, 1992), when platinum(II) chloride or platinum(IV)chloride (up to 100 mg Pt/kg diet) was given in the diet of lactating rats (21 days) (Kirchgessner and Reichlmayr-Lais, 1992). In contrast, single oral (gavage) doses of platinum(IV)sulphate (200 mg Pt/kg bw) caused a reduction of pup

weights when administered to female Swiss ICR mice at gestational day 7 or 12, and a decreased activity when administered at lactational day 2. Single subcutaneous treatment with sodium hexachloroplatinate(IV) (20 mg Pt/kg bw) only resulted in decreased pup activity when administered on gestational day 12 (D'Agostino et al., 1984).

Platinum(IV)chloride (total dose: 16 mg Pt/kg bw) administered subcutaneously for 30 days to male Swiss mice or intratesticularly once to male albino rats resulted in largely decreased testis weights in both species and in spermatogenic arrest in mice and total testicular necrosis and destruction of all spermatozoa in rats (Kamboj and Kar, 1964). *In vitro* experiments (human spermatozoa; rat Sertoli cells) (Hostynek et al., 1993; HSE, 1985) indicate that soluble platinum compounds may influence sperm function by induction of spermatogenic arrest and the acrosome reaction, reduction of the sperm motility, and effects on Sertoli cells (indirect effect).

Recommendations

Platinum metal and insoluble platinum compounds

Very few data are available regarding effects in humans following exposure to platinum metal or insoluble platinum compounds. One case of dermatitis due to a platinum ring and one case of stomatitis has been described. Further, the presence of both type I (immediate) and type IV (delayed) hypersensitivity has been reported in some workers exposed to "platinum dichloride".

No data in experimental animals were found on sensitising or eye irritating properties of platinum metal or its insoluble compounds. Platinum(IV)oxide and platinum(II)chloride were not irritating to the skin. Neither acute nor repeated inhalation data on platinum metal or its insoluble compounds were found. Oral LD_{50} values in rats for platinum(IV)oxide were greater than 3.4 g/kg bw (>2.9 g Pt/kg bw). No significant effects on body weight gain, haematological parameters or plasma creatinine was shown in a study in male rats, when platinum(II)chloride was added in the diet (50 mg Pt/kg diet) for 4 weeks, at doses *corresponding to around 5 mg Pt/kg bw/day (Reichlmayr-Lais et al., 1992)*.

Data on carcinogenicity are lacking.

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

No effects were seen in rat fetuses (weight, resorptions, malformations) following daily administration of doses of platinum metal of 0.1-100 mg/kg diet, for four weeks before pregnancy to gestational day 20 or in offspring (weight, haematology) following administration of similar daily doses of platinum(II) chloride during lactation.
In conclusion, SCOEL is of the opinion that the data on the toxicity of platinum metal and insoluble platinum compounds are insufficient to allow recommendation of a health-based occupational exposure limit.

Soluble platinum compounds

Human data showed that the most significant risks from occupational exposure to water-soluble platinum salts are respiratory sensitisation and skin effects. Symptoms include lachrymation, irritation of the upper respiratory tract, rhinitis, asthma and coughing, as well as angioedema and urticarial and eczematous skin lesions. The prevalence of respiratory and/or cutaneous symptoms among workers involved in platinum refinery was frequently over 50% of the work force, but has decreased during the last decades. Further, data indicate that platinum compounds with a halide ligand coordinated to platinum (i.e., chloroplatinates, such as hexachloroplatinic(IV) acid and the hexa- and tetrachlorplatinates) provoke allergic reactions while other soluble complexes having ligands other than halogens (e.g., tetraammineplatinum dichloride), do not. Linnett and Hughes (1999) for instance, found that the cumulative chance of becoming sensitised after 5 years of exposure was 0% in a department with exposure to only tetraammineplatinum dichloride and 51% in a department with exposure to only chloroplatinate exposure and 33% for mixed exposure. After skin prick testing with chloroplatinates, an immunological type I reaction has been established, also other tests indicated an IgE-mediated reaction. In the five-year prospective cohort study by Merget and co-workers (2000; 2001; Merget, 2000) sensitisation did not occur at exposure levels below 10 ng/m^3. Sensitisation after 5 years of exposure to platinum salts appears to be rare (Merget et al., 2001). Therefore, SCOEL concluded that exposure to chloroplatinates at levels below 10 ng/m^3 is not expected to cause sensitisation. The results of the Linnett and Hughes (1999) study indicated that exposure to levels of tetraammineplatinum dichloride mostly below 0.5 µg/m^3 but occasionally higher than 2 or 10 µg/m^3 did not result in allergic reactions. No other effects have been reported in workers occupationally exposed to soluble platinum compounds.

Gastroenteritis and acute renal failure was seen in a man who ingested 600 mg of potassium tetrachloroplatinate(II) (corresponding to around 8 mg/kg bw or 4 mg Pt/kg bw).
Experimental animal data indicated that soluble platinum compounds are irritating to the skin and irritating or even corrosive to the eyes. Experiments in rodents confirm the findings

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

Acute inhalation data were not found. Oral LD_{50} data for chloroplatinates in rats range from ca. 10 to 100 mg Pt/kg bw. Repeated inhalation studies were limited to studies investigating differences in immunologic parameters and effects in the airways in monkeys. Effects on body weight gain (decreased) and relative kidney weight (increased) were seen after four weeks of repeated oral administration of platinum(IV)chloride at doses of ca. 40 mg Pt/kg bw/day. Similar exposure to 5-10 mg Pt/kg bw/day did not affect body or kidney weights, although an increase in plasma creatinine content was seen in one study. Decreases in haematological values (erythrocytes, hematocrit) were seen in male, but not in female rats at these lower dose levels.

Data on carcinogenicity are lacking.

Numerous soluble platinum compounds have been tested for their mutagenic activity *in vitro* in bacterial and mammalian cell systems, mostly without metabolic activation, and in fruit flies. Many of the compounds were positive. Some of the compounds were tested for other endpoints in other systems (*E. coli*: SOS chromotest; *B. subtilis*: rec assay; human lymphocytes/leukocytes: micronucleus test and comet assay), inducing both positive and negative results.

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

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

Human and animal data indicate that soluble chloroplatinates are sensitising agents. SCOEL is of the opinion that health-based occupational exposure limits can be recommended for allergens if adequate data on the existence of a threshold are present for the compound concerned. For the sensitising properties of ammonium hexachloroplatinate, the five-year prospective cohort study by Merget and co-workers (2000; 2001; Merget, 2000) suggest that at exposure levels below 10 ng/m^3 sensitisation is

not to be expected. SCOEL noted, however, the lack of quantification of peak exposures, that high exposures may have occurred in the past which could have contributed to the sensitisation cases, that the exposure estimates were not based on personal sampling and the highly variable exposures, all of which may have lead to unreliable exposure estimates. The data from Linnett and Hughes (1999) and Steinfort et al., (2008) indicated that exposure to levels of tetraammineplatinum dichloride mostly below 0.5 µg/m^3 but occasionally higher than 2 or 10 µg/m^3 does not result in allergic reactions. However, these data cannot be used for deriving an OEL for soluble platinum compounds because a no-effect level could be (much) higher than 10 µg/m^3.

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

In conclusion, SCOEL is of the opinion that the database does not allow the recommendation of an OEL for soluble platinum compounds.

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