IPA
INTERNATIONAL PLATINUM GROUP METALS ASSOCIATION

6

TOXICITY OF PLATINUM AND PLATINUM COMPOUNDS (WITH SUMMARIES FOR OTHER PGMs)

CONTENTS

CONTENTS

SUMMARY

- The main health effect of concern for certain forms of platinum (Pt) in industrial settings is respiratory sensitisation, often referred to as "platinum salt sensitivity" or PSS.

- Not all forms of platinum are respiratory sensitisers. Only those platinum compounds which possess labile leaving groups coordinated to Pt have been shown to be respiratory sensitisers.

- Species that are respiratory sensitisers in industrial settings are largely confined to complex halogenated platinum salts (CHPS). Table 6-2 categorises the potential of various forms of Pt for this adverse effect.

- Sensitisation is believed to commence when a platinum complex (hapten) binds to a protein, presenting the key antigenic stimulus to the immune system. Antibodies, most often immunoglobulin E (IgE), mount a response to the antigen—this reaction is also the basis of the diagnostic test for PSS (via skin prick testing).

- Induction of sensitisation in workers is considered to be predominantly via inhalation, but dermal exposure may also be important. Factors that may predispose workers to PSS include smoking, genetic influences, and co-exposure to other respiratory irritants.

- Workers exposed to CHPS who become sensitised are initially asymptomatic; the period between first exposure and sensitisation is typically between several months and 3 years.

- Once sensitised, workers with continued exposure usually progress from mild to increasingly serious reactions. Clinical features often begin with conjunctivitis and/or rhinitis, progressing to bronchial/asthmatic effects including tightness of the chest and shortness of breath.

SUMMARY

- The exposure required to elicit an allergic reaction in a sensitised individual is often considerably lower than that needed for induction.
- In early epidemiology studies, sensitisation prevalence rates were up to 50% or greater, but due to greater awareness of PSS and efforts by the PGM industry to reduce exposures, current prevalence rates are typically below 10%.
- Other potential health effects relevant to industrial workers are dependent on the form of platinum involved (see Table 6-3).
- Health care workers (HCWs) may also be exposed to allergenic Pt-containing anticancer drugs (platins). Sensitisation reactions have been observed in patients being administered platins, but not to date in HCWs, given that their exposures are normally low compared to patients. However, the potential for toxicities must be borne in mind.
- The toxicology profiles of the other PGMs (viz. palladium, rhodium, iridium, ruthenium and osmium) and their industrially important compounds are varied (see Table 6-4). However, none is known to be a significant respiratory sensitiser.

Note: Within this chapter, prominence has been given to the respiratory sensitisation potential of certain platinum species as this health effect is particularly relevant to occupational exposures and, thus far, constitutes the effect of most concern. The key information on this topic is presented within Section 6.1, and its sub-sections. Other potential adverse effects associated with various platinum compounds are addressed in Section 6.4. A brief summary of the toxicology profiles of the remaining platinum group metals (PGMs) and their compounds is provided at the end of this chapter (Section 6.5). For quick reference purposes, Table 6-2 provides a summary categorization of the respiratory sensitising potential of industrially important Pt substances. As legal requirements are constantly evolving, readers have to make sure to comply with all applicable laws and regulations when implementing or revising workplace monitoring processes.

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RESPIRATORY SENSITISING PLATINUM SPECIES

In focusing on sensitisation it is important to note that not all forms of platinum are respiratory sensitisers. Sensitisation depends largely on the chemical reactivity (which is related to structure) and the bioavailability of the platinum species in question. Those compounds that have been shown to be respiratory sensitisers possess labile leaving groups which are readily displaced by sulphur- or nitrogen-containing ligands on proteins, *i.e.*, they act as a hapten to form an allergenic protein complex. Conversely, those species that are too chemically inert, insufficiently bioavailable, and/or have firmly bound leaving groups that cannot be readily displaced do not induce sensitisation. Although the solubility (linked to bioavailability) and charge of a compound may play a role with respect to sensitisation, they are not major determinant factors.

All platinum compounds that are known respiratory sensitisers produce allergic reactions in which both the respiratory tract and skin are involved, though the former predominates. These reactions are caused by a humoral immune response, typically associated with increased levels of IgE, and thought to be linked to an initial Th2-type cytokine release (WHO, 2000; Dearman *et al.*, 1998; Ban *et al.*, 2010; Kimber *et al.*, 2014; see Section 6.3 for further discussion). Attributes typical of a Type I (IgE) immediate-type hypersensitivity reaction include a symptom-free latency period and increased sensitisation over time, with sensitised subjects reacting to lower exposure levels (elicitation) than the levels required to induce sensitisation (IPCS, 1991). The platinum species discussed below are reviewed with respect to these attributes.

COMPLEX HALOGENATED PLATINUM SALTS

Complex halogenated platinum salts (CHPS) are compounds where the halide is directly coordinated to a central Pt atom. Those compounds that specifically contain chlorine, such as ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$] or sodium tetrachloroplatinate (Na_2PtCl_4), are often referred to as "chloroplatinates." But CHPS, as a class, can include other halogens such as bromine and iodine as well (see Chapter 2). While all these salts are water-soluble and bioavailable in biological media, the most salient feature with respect to their sensitisation potential relates to the fact that the bonds between the halide groups and the Pt atom are weak, leading to ligand substitution with proteins and, thus, the formation of protein antigens (Cleare *et al.*, 1976; Linnett and Hughes, 1999). Currently, exposures to CHPS are predominantly found in refining and platinum production sectors, as well as in a few other downstream users such as chemists and technicians. The most industrially important of these salts are discussed in Chapter 2.

HUMAN STUDIES

The first reliably documented study of sensitisation to CHPS occurred in the early-1900s, when exposure to paper prepared with potassium chloroplatinate was shown to cause violent sneezing, coughing, and cracked and itchy skin in a group of photographic workers (Karasek and Karasek, 1911). In a later cross-sectional study by Hunter *et al.* (1945),

[1] A full review of the toxicology of platinum and its compounds is beyond the scope of this chapter and other sources should be consulted (e.g., IPCS, 1991; WHO, 2000; HCN, 2008; SCOEL, 2011).
[2] Synonymous with platinum salt sensitisation.

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frank effects associated with asthma—including tightness in the chest, wheezing, and shortness of breath—as well as rhinitis (inflammation of nasal mucosa resulting in a runny nose and sneezing) and urticaria (skin wheal-and-flare reaction), were seen in workers exposed to ammonium hexachloroplatinate in the refining of platinum. Since these early reports, numerous studies in workers including Venables *et al.* (1989), Baker *et al.* (1990), Bolm-Audorff *et al.* (1992), Calverley *et al.* (1995, 1999), Niezborala and Garnier (1996), Linnett and Hughes (1999), Merget *et al.* (2000), Cristaudo *et al.* (2005), and Heederik *et al.* (2016) have reported on the sensitising effects of these salts.

On a weight-of-evidence basis, it is possible that induction of respiratory sensitisation in humans may also occur through dermal exposures as has been demonstrated in animal studies on CHPS (see the next section) and for other chemical allergens of both low- and high-molecular weight (Karol *et al.*, 1981; Rattray *et al.*, 1994; Liu *et al.*, 2000; Arts *et al.*, 2006; Tarlo and Malo, 2006; Redlich, 2010; Kimber *et al.*, 2014).

Symptoms of conjunctivitis, rhinitis, dyspnoea (breathlessness), asthma, and urticaria feature to various degrees in most occupational studies that have been conducted on CHPS, with asthma and rhinitis constituting the most prevalent of these symptoms (Merget, 2000). Numerous terms have been used to describe the array of symptoms associated with exposure to CHPS. For purposes of this Guide, the most widely-used term—"platinum salt sensitivity" or PSS (Calverley *et al.*, 1995)—is used to characterise these effects. Diagnosis has been based on a number of endpoints including evidence of exposure-related symptoms; positive responses to skin prick tests (SPT) and/or bronchial challenge; and, decreases in lung function as measured by spirometry (Linnett and Hughes, 1999; Merget, 2000). These endpoints are discussed more thoroughly in Chapter 7 (Health Surveillance of Workers).

Workers exposed to CHPS and who become sensitised experience a period in which they are asymptomatic (IPCS, 1991; Merget, 2000). Latencies between first exposure and sensitisation typically last several months to several years (Pepys *et al.*, 1979; Merget *et al.*, 1988; Merget, 2000), with approximately 80-90% of PSS cases detected by SPT occurring within 5 years of exposure onset (Linnett and Hughes, 1999). But occasionally latencies as short as one or two weeks (Dally *et al.*, 1980; Pepys *et al.*, 1979) or as long as 10 years or more have been reported (Bolm-Audorff *et al.*, 1992; Merget, 2000).

Once sensitised, workers with continued exposure typically show progression from moderate to severe asthma (Merget *et al.*, 1999; Merget, 2000), but progression depends on the stage at which PSS is diagnosed and the steps taken to reduce worker exposures. Several studies have shown that with early detection and removal from the workplace environment in which exposure is occurring, workers in the formative stages of sensitisation may be safeguarded against the development or progression of chronic symptoms of asthma and bronchial hyper-reactivity (Merget *et al.*, 2001; Assoufi *et al.*, 1997). But in workers with clear manifestations of bronchial hyperreactivity (*i.e.*, those later in the course of disease), as many as half continue to have symptoms of asthma even following termination of employment (Baker *et al.*, 1990; Merget *et al.*, 1994, 1999). The exposure level required to elicit an allergic reaction is often considerably lower than the induction concentration that originally resulted in sensitisation (Rosner and Merget, 2000; Arts *et al.*, 2006; see Chapter 7 on Health Surveillance for further discussion). While early studies showed sensitisation prevalence rates as high as 50% or greater (Hunter *et al.*, 1945; Roberts, 1951), due to greater awareness of PSS and associated efforts by the industry to lower exposures, current prevalence rates of sensitisation are generally below 10% (Merget *et al.*, 2000; Heederik *et al.*, 2016).

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Several factors have been noted to predispose workers to the development of PSS including atopy (a predisposition toward the development of immediate hypersensitivity reactions to common environmental allergens), cigarette smoke and other respiratory irritants, and genetics.

The evidence for atopy as a risk factor was first identified in the early-1970s in a group of platinum refinery workers (Dally *et al.*, 1980). In this group of workers, atopics were noted to have an increased rate of leaving employment, though not all atopics had PSS. The finding by Dally and co-workers constituted the basis for the general exclusion of atopics from the workforce in many platinum refineries (Hughes, 1980). In a later study on essentially the same workers, both atopy and cigarette smoking were studied as risk factors for PSS (Venables *et al.*, 1989). The risk from atopy [Relative Risk (RR)=2.29; 95% Confidence Interval (CI)=0.88-5.99] was smaller than that from smoking (RR=5.05; 95% CI=1.68-15.2) and was not significant when adjusted for smoking. However, these findings were based on a relatively small cohort (n=91). In a more recent study involving a much larger cohort of workers employed in five primary and/or secondary refineries (n=1040), the RR from atopy was reported to be around 1.8 (95% CI=1.2-2.8) [Heederik *et al.*, 2016]. Although this risk estimate is based on a larger sample size, it should be borne in mind that some of the refineries participating in the Heederik study had pre-employment practices excluding atopics, resulting in a risk estimate that may have been negatively skewed.

As observed in the Venables *et al.* study, as well as other reports, the evidence for smoking as a risk factor for PSS has been more compelling than that for atopy. Earlier studies (Calverley *et al.*, 1995; Niezborala and Garnier, 1996) suggested that smoking could increase the risk of PSS by factors ranging from 4.9 to 8.0. However, as was the case for atopy in the Venables study, the estimated risk ratios are highly uncertain in these studies (95% CIs of 2.6-25 and 1.4-18, respectively) because of the relatively small worker populations on which they were based (n≈80). In the recent study by Heederik *et al.* (2016), the estimated risks associated with smoking were increased approximately two-fold (RR=1.9; 95% CI=1.2-2.8). Although the disparities among risk estimates could be simply a matter of sampling uncertainty, they may also relate to pre-employment selection differences among study populations, as knowledge of smoking as a specific risk factor has become more widely recognised, and because smoking in the workplace has been increasingly discouraged as general practice.

Co-exposure to respiratory irritants other than cigarette smoke—such as those found in the workplace in conjunction with CHPS (e.g., chlorine, acid gases, ammonia, etc.)—may also potentiate the development of PSS (Venables et al., 1989; Baker et al.,1990). Similar potentiating effects have been seen between CHPS and ozone in non-human primates (Biagini *et al.*, 1986; see below and Section 6.3). This linkage with pro-inflammatory co-exposures, including tobacco smoke, is consistent with the so-called "Danger Hypothesis" of response to allergens (Matzinger, 2002). Finally, genetics may factor into the development of PSS. In a group of refinery workers (n=44), Newman-Taylor *et al.* (1999) showed that the human leukocyte-associated antigen (HLA) phenotype was a significant determinant of sensitisation to ammonium hexachloroplatinate.

Despite the many studies conducted on CHPS workers, robust exposure-response data suitable for estimating a human sensitisation induction threshold are currently lacking. Most studies grouped workers by workplace site, utilising these sites as surrogates of exposure. As a result, exposure data were either not reported or simply characterised as low, medium, or high depending on job classification or where the worker spent the most time. However, four studies do present exposure data (Table 6-1, page 9), and

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REFERENCE	STUDY CHARACTERISTICS	EXPOSURE DATA µg SOLUBLE Pt/m^3	PREVALENCE OF SENSITISATION (%) IN WORKERS	COMMENTS
Baker *et al.*, 1990; Brooks *et al.*, 1990	Secondary Refinery Cross-sectional Total Participants: 136	n = ~ 75; Stationary GM: 0.4–27., 8-hr TWA Period: 4 months during 1977-1979	Current: 15/107 (14) 1981 Former: 8/29 (28) 1971-1979	• Most areas associated with production had elevated air concentrations of CHPS; average air concentrations frequently (up to 70% of the time) exceeded 2 µg/m^3.[a] • 73% of current sensitised workers worked in production areas or maintenance.
Linnett and Hughes., 1999	Secondary Refinery., TPC[b] Laboratory., and Autocatalyst (Autocat) Plant Retrospective 1976-1991 Total Subjects: 547 Total CPOs[c]: 341	CPOs Refinery n = 380; Personal < 0.5 (88%)., short-term ≥ 2 (2%)., short-term CPOs TPC Laboratory n = 130; Personal < 0.5 (52%)., 8-hr TWA ≥ 2 (28%)., 8-hr TWA CPOs Autocat n = 176; Personal < 0.5 (61%)., 8-hr TWA ≥ 2 (3%)., 8-hr TWA Period: 1989-1991	Refinery CPOs 106/270 (39) Laboratory CPOs 5/31 (16) Autocat CPOs 0/39 (0)	• There was a strategic bias towards sampling of tasks of short duration in the refinery in order to identify peak exposures. • Despite higher exposures to total soluble Pt in the TPC laboratory than the refinery (due to the presence of soluble compounds which were not CHPS) laboratory workers may have been exposed to lesser quantities of sensitising Pt compounds than refinery workers, possibly contributing to their lower prevalence of sensitisation. • Despite higher exposures to total soluble Pt in the Autocat than the refinery, due to the absence of CHPS in the Autocat, workers exposed solely to TPC failed to show any evidence of platinum sensitivity.
Merget *et al.*, 2000 Merget., 2000	Catalyst Production Plant Prospective 1989-1995 Total Subjects: 275	n = 22[d]; Personal Median: 0.177., based on 5/115 subjects Period: 1993 n = 56; Stationary Median: 0.00005-0.037 Period: 1992/93	Production line and related workers: 13/115 (11) All other workers: 1/160 (< 1)[e]	• Concentrations of soluble Pt in stationary and personal air samples were highly variable. • Concentrations reported were based upon very few measurements. • The authors noted, that based on the study design., no valid threshold for occupational hygiene purposes could be established from the results. However, extremely low exposures (~ 0.01 µg/m^3) did not result in the development of sensitisation.
Heederik *et al.*, 2016	Primary and Secondary Refineries (5) Retrospective 2000-2010 Total Subjects: 1036	n = 1607; Personal GM: 0.079-0.219; 8-hr TWA Period: 2000-2010	Newly hired 98/1036 (9)	• ~8.5% of samples exceeded 2 µg/m^3. • Recent exposures seemed to be more predictive of sensitisation than average or cumulative exposures. • While "recent" exposures < 0.2 µg/m^3 (on average) appeared capable of inducing sensitisation, due to the high variability in the distribution of workplace measurements, a substantial percentage of daily exposures exceeded 1 µg/m^3.

GM = Geometric Mean.
a. The current Threshold Limit Value (TLV) set by the American Conference of Industrial Hygienists (ACGIH) for soluble Pt.
b. TPC = Tetraammine platinum dichloride. Exposures in this laboratory were to a mix of TPC and CHPS.
c. CPO = Chemical Process Operators.
d. While 22 personal samples were reported in the paper, the raw data show that only 18 samples were taken. Only 5 out of 115 subjects agreed to be personally monitored.
e. The sensitised worker in this group did have occasional exposure to CHPS.

Table 6-1: Summary of Key Epidemiology Studies of Workers Exposed to Platinum Compounds.

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although of varying quality, these do warrant further consideration.

Of the four studies shown in Table 6-1, one was cross-sectional (Baker *et al.*, 1990), two were retrospective (Linnett and Hughes, 1999; Heederik *et al.*, 2016), and one was prospective (Merget *et al.*, 2000). While prospective studies are generally considered more scientifically robust than other studies (due to the ability to better correlate effects and their associated exposures as they occur), the single prospective study (Merget *et al.*, 2000) had a limited exposure dataset based upon few measurements, most of which were area (static) air monitoring rather than personal samples. Such measurements typically tend to underestimate workers' exposures (Cherrie, 2003; Vincent, 2007). The two retrospective studies (Linnett and Hughes, 1999 and Heederik *et al.*, 2016) had far larger study populations and considerably more measurements, all of which were obtained with personal samplers. However, the Linnett and Hughes study presented exposures in increments of 0.5 µg soluble Pt/m^3 (*i.e.*, no specific concentrations were provided) and the Heederik *et al.* study failed to fully account for potential short-term exposures (see discussion below). The fourth study was cross-sectional (Baker *et al.*, 1990), constituting a snap-shot in time, and had the fewest subjects (comprising only workers who agreed to participate in the study) and the lowest number of measurements, all of which were area samples.

None of these studies identified a threshold level for sensitisation. In the Baker *et al.* (1990), Linnett and Hughes (1999), and Heederik *et al.* (2016) studies sensitization was found at the lowest average exposure levels reported (see Table 6-1). While exposures were fairly high in the Baker *et al.* study, they appeared to be much lower in the latter two studies, i.e. most measurements were below the current Threshold Limit Value (TLV) of 2 µg soluble Pt/m^3 set by the American Conference of Governmental Industrial Hygienists (ACGIH) for soluble platinum salts (ACGIH, 2013). Prevalence of sensitisation in workers most likely exposed to CHPS ranged between 9 and 39% across the three studies, with the most recent study showing the lowest rate of prevalence. This drop may be due, in part, to the continuing effort on the part of the platinum industry to keep CHPS exposures as low as practically possible. In the Merget *et al.* (2000) study, which relied largely on area sampling measurements, workers exposed to very low levels of CHPS (~ 0.01 µg Pt/m^3 as soluble Pt) appeared to be without risk to sensitisation, whereas workers exposed to median concentrations of ~ 0.1 µg Pt/m^3 had a prevalence rate of sensitisation around 11%. However, as exposures were highly variable and, most likely, significantly under-estimated, none of the exposures reported should be seen as representing definitive no observable adverse or lowest observable adverse effect levels (NOAELs or LOAELs) for sensitisation.

Exposure-response relationships were comprehensively evaluated only in the Heederik *et al.* (2016) study. The authors provided substantive evidence of an initial steep linear increase in risk at the lowest average exposures recorded that levelled off at average exposures around 0.2 µg soluble Pt/m^3. No threshold was established for the induction of sensitisation. Estimated exposures occurring closest to the point in time at which positive skin prick tests were observed were found to be more predictive of sensitisation than were cumulative exposures. However, the time-specific exposure estimates for individual workers in this study may be unreliable in terms of linkage to the observed increased risks as they were based on geometric means of 8-hour time weighted average (TWA) daily workplace exposures, which were highly variable. As a consequence, significant proportions of workers in a workplace with a low estimated geometric mean exposure were actually exposed to much higher 8-hour TWA concentrations (*e.g.*, 5% of workers with a geometric mean exposure of ≈0.04 µg/m^3 were exposed to 8-hour TWAs

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that were above 1 µg soluble Pt/m^3). It is, therefore, quite plausible that the observed risks in workers at the low end of the exposure scale (who were classified as such based on their geometric mean exposure) were due to substantially higher platinum concentrations to which some of these workers had actually been exposed.

Other researchers (Morris, 1994; Nieuwenhuijsen *et al.*, 1995) and regulatory/quasi-regulatory authorities (WHO, 2000; HSE, 2001) have suggested that peak, short-term exposures may play an important etiological role in the risk from various respiratory sensitisers. It is unknown whether the high variability of the daily measurements in the Heederik *et al.* study may actually represent extremely high short-term excursions from geometric mean daily exposure levels or sustained day-long variations. In either case, it is clearly essential that this feature of the exposure data is taken into account in characterising the shape of the exposure-response and assessing evidence of response thresholds (or lack thereof).

Overall, data from human studies clearly establish a causal link between CHPS exposure and PSS, however, to date, it is not possible to reliably establish a threshold level for sensitisation.

NON-HUMAN TOXICOLOGY STUDIES AND MECHANISTIC INVESTIGATIONS

Most animal studies on CHPS sensitisation have involved either dermal, intradermal, or parenteral (systemic injection) administration, the latter route of exposure being of lesser relevance to occupational exposures. Nevertheless, overall, these studies support the findings seen in humans. A few studies have also been conducted via inhalation.

In a series of sub-chronic inhalation and percutaneous studies conducted on non-human primates (cynomolgus monkeys), Biagini and co-workers failed to show any primary sensitivity or changes in pulmonary function in animals administered various doses of sodium hexachloroplatinate (Na_2PtCl_6) (Biagini *et al.*, 1983). Although further challenge with Na_2PtCl_6 resulted in increased pulmonary hyperreactivity, no clear dose-response could be established, possibly due to the small number of animals studied. In a follow-up study, Biagini and co-workers tested the synergistic effects of ozone on ammonium hexachloroplatinate [$(NH_4)_2PtCl_6$] in the same species of primates (Biagini *et al.*, 1986). Those animals receiving either agent alone failed to show primary sensitivity, but those receiving both ozone and $(NH_4)_2PtCl_6$ had significant allergic dermal hypersensitivity and pulmonary hyperreactivity upon re-challenge with Na_2PtCl_6. These results support the hypothesis advanced by others (Venables et al., 1989; Baker et al., 1990) that airway damage from irritant materials may potentiate PSS induction in CHPS-exposed workers (see Section 6.1 and Section 6.3 for further discussion).

Positive results have also been seen in several strains of mice administered CHPS via subcutaneous or dermal exposure (Schuppe *et al.*, 1992; Schuppe *et al.*, 1997a,b; Dearman *et al.*, 1998; Kimber and Dearman, 2005; Ban *et al.*, 2010; Williams *et al.*, 2015). The CHPS tested included the hexachloroplatinate salts Na_2PtCl_6 and $(NH_4)_2PtCl_6$, as well as several tetrachloroplatinate salts, viz. $(NH_4)_2PtCl_4$, Na_2PtCl_4, and K_2PtCl_4. Various indicators of immunologic responses were studied including lymph node cell proliferation, induction of certain cytokines and increases in total serum IgE. All compounds showed evidence of being capable of inducing immunological responses characteristic of respiratory sensitisation. Several of the studies showed that immunologic responses seen in various mice were mediated by a class of cytokines produced by specific T-helper cells (Th2) which are associated with

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immediate-type hypersensitivity in humans, including respiratory sensitisation responses (see Section 6.3). The studies also demonstrated the potential for skin exposures to CHPS to induce respiratory sensitisation, including circumstances where induction exclusively via the dermal route was then followed by respiratory system challenge (Williams *et al.*, 2015). Parenteral administration of $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ in rats and intranasal instillation of Na_2PtCl_6 in mice have also provided evidence of sensitising effects similar to those seen in the animal studies above, as well as humans (Murdoch and Pepys, 1984a,b; 1985; 1986; Ban *et al.*, 2010).

PLATINUM ANTICANCER DRUGS

The second group of platinum-containing compounds that have shown evidence of systemic sensitisation reactions, thought commonly to be mediated by IgE, are those used in the treatment of cancer—including cisplatin, carboplatin, and oxaliplatin, which are often generically referred to as "platins." Unlike industrial process exposures involving CHPS, clinical use of these platins typically involves parenteral administration (injection) to patients (Calvert *et al.*, 1993; Hewitt, 1997), although more recently, some of these drugs have been administered via inhalation in aerosolised forms (Wittgen, 2006). Nevertheless, like CHPS, the sensitising properties of platins relate to the displacement of the leaving groups within these compounds with sulphur- or nitrogen-containing ligands on proteins (see Section 6.3).

Workers manufacturing platins, as well as health care providers (physicians, nurses, pharmacists, etc.) and janitorial staff can be exposed to platins via dermal contact, inhalation, and/or ingestion (*e.g.*, through hand-to-mouth contact) in the course of their daily routines (Hewitt, 1997; Connor and McDiarmid, 2006; Villarini *et al.*, 2011). It is important to keep in mind that what is known about the sensitising effects of platins in humans is based exclusively on studies of patient populations where the doses administered are typically high (maximum tolerated doses or MTDs) and intermittent, and with markedly differing toxicokinetics to inhalation and dermal exposures (especially related to absorption) as noted in Chapter 5 on Toxicokinetics. Thus, the extent to which the effects discussed below in patients are relevant to workers exposed to platins in occupational settings is uncertain.

HUMAN STUDIES

The platins are used to treat a variety of cancers, including cancer of the ovary, uterus, testis, bladder, skin, breast, liver, and stomach to name a few (IARC, 1981; 1987a). Because the doses administered are necessarily high in order to provide therapeutic benefit, they unfortunately can also produce a variety of adverse toxic effects in multiple target organs, including sensitisation (Shepherd, 2003; Hartmann and Lipp, 2003; Brandi *et al.*, 2003). Early symptoms of sensitisation can be similar to those seen in CHPS-exposed workers, including wheezing, shortness of breath, and skin rashes; these usually resolve quickly upon administration of antihistamines and corticosteroids (McKeage, 1995; Makrilia *et al.*, 2010). But with increasing infusions, symptoms can become more severe, including life-threatening anaphylactic responses (Polyzos *et al.*, 2001; Shepherd, 2003; Makrilia *et al.*, 2010). Due to the increasing use of these drugs over the past decade, sensitisation rates in patients as high as 20 to 40% have been reported for platins (Makrilia et al., 2010).

With respect to evidence of occupational exposures, platins have been found in urine and/or blood samples taken from various health care workers (HCWs) involved in the treatment of

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patients (Nygren and Lundgren, 1997; Pethran *et al.*, 2005) and from hospital pharmacists (Pethran *et al.*, 2003; Mason *et al.*, 2005) involved in preparation and handling of platin drugs. In the case of the pharmacists, exposures to platins were both dermal and via inhalation. But in the case of the HCWs, exposures were primarily dermal, lending credence to the importance of this route occupationally and in terms of possible systemic effects. A variety of symptoms have been reported in HCWs handling chemotherapy drugs (McDiarmid and Egan, 1988; Valanis *et al.*, 1993; Krstev *et al.*, 2003). While some of the symptoms could potentially be indicative of sensitisation (*e.g.*, airway irritation and skin rash), none has been specifically tied to exposures to platins, nor has respiratory sensitisation been diagnosed (Hewitt, 1997; Connor and McDiarmid, 2006). Moreover, studies have shown that inadequate ventilation in hospital oncology units and exposure to chemicals present in cleaning and personal hygiene products have been associated with the types of upper respiratory symptoms reported by chemotherapy HCWs (NIOSH, 2014).

Numerous studies have shown the importance of using personal protective equipment and good work practices in mitigating exposures to platins and other anticancer drugs in HCWs (Hewitt, 1997; Mason *et al.*, 2005; Connor and McDiarmid, 2006; Villarini *et al.*, 2011; NIOSH, 2014)—see Chapter 9 for further discussion regarding Control Measures and Management Systems. A case of occupational asthma was reported in a worker producing cytotoxic drugs, but the cause of asthma was attributed to exposure to potassium tetrachloroplatinate in the production of the drugs (Thanasias *et al.*, 2013).

NON-HUMAN TOXICOLOGY STUDIES AND MECHANISTIC INVESTIGATIONS

In addition to studying the sensitising effects of various CHPS, Schuppe *et al.* (1992), Dearman *et al.* (1998), and Murdoch and Pepys (1984b) also studied the effects of cisplatin on mice and rats. As was the case for CHPS, dermal exposure to cisplatin (cis-$[(NH_3)_2PtCl_2]$) increased the production of Th2 cytokine markers (Dearman *et al.*, 1998) and cell counts in lymph nodes (Schuppe *et al.*, 1992). However, in both studies, the primary lymph node response to cisplatin appeared weaker than it was for various CHPS. Murdoch and Pepys (1984b) reported similar responses for cisplatin in their injection studies on rats.

6.2

PLATINUM SPECIES THAT ARE NOT RESPIRATORY SENSITISERS OR POSSESS UNCERTAIN SENSITISING POTENTIAL

PLATINUM SPECIES THAT ARE NOT RESPIRATORY SENSITISERS OR POSSESS UNCERTAIN SENSITISING POTENTIAL

As highlighted in the introduction to this chapter, not all forms of platinum have been shown to be respiratory sensitisers in humans. This is due to the fact that some species are either too chemically inert or insufficiently bioavailable to make them effective allergens. Others have ligands too strongly bound to the Pt atom to become sensitisers. Conversely, some species, while bioavailable, fail to trigger the cellular mechanisms required to induce respiratory sensitisation (see Section 6.3 for further discussion on Mode of Action). Lastly, there are some compounds which, while showing evidence of certain biological activity in toxicologic studies and/or indications of sensitisation in mechanistic investigations, have largely failed to induce respiratory sensitisation in workers exposed to them. The most important platinum species that fall under these four categories are discussed below.

CHEMICALLY INERT/ LOW BIOAVAILABLE PLATINUM SPECIES

Elemental platinum and platinum alloys are considered to be too chemically inert and non-bioavailable to induce sensitisation. Certain non-halogenated simple platinum salts (*e.g.*, oxidic/sulphidic compounds) are either insufficiently bioavailable (due to their insolubility) and/or are not structurally configured to be protein reactive. As such, these forms of platinum have failed to induce immunological responses in humans, as discussed below.

HUMAN STUDIES

In an early study on refinery workers (Hunter *et al.*, 1945), workers exposed to fine platinum particulate ("sponge") in sieving—where CHPS would have been absent—showed no evidence of PSS. Although no formal epidemiological studies on elemental platinum have been conducted since that time, the frank sensitising effects that have been observed in certain workers and patients exposed to CHPS and platins, respectively, have been notably absent in workers exposed to platinum (in a variety of forms from massive to fine particles), as well as to platinum alloys, and/or oxidic and sulfidic platinum salts. This includes workers from a wide range of industry sectors including refining, deposition of elemental Pt on substrates, manufacture of Pt articles (*e.g.*, jewellery, gauzes, medical devices) and bullion handling.

NON-HUMAN TOXICOLOGY STUDIES AND MECHANISTIC INVESTIGATIONS

As part of a series of studies on the sensitisation potential of various platinum species (see above) Schuppe and colleagues examined the sensitising properties of

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PLATINUM SPECIES THAT ARE NOT RESPIRATORY SENSITISERS OR POSSESS UNCERTAIN SENSITISING POTENTIAL

elemental Pt and PtO_2 on the lymph nodes of mice (Schuppe *et al.*, 1993). Unlike CHPS and cisplatin, they found no evidence of sensitisation reactions in mice for these chemically inert, low bioavailability platinum species. Aside from studies of artificially produced protein-conjugates which are not directly relevant to occupational exposures (IPCS, 1991), no other animal or mechanistic studies have been conducted on these species.

PLATINUM SPECIES WITH LIGANDS STRONGLY BOUND TO Pt

Platinum species which have ligands strongly bound to the Pt atom are also unlikely to induce sensitisation due to an absence of exchange substitution with N- and S- centres in proteins. A prototypic compound class are the tetraammine Pt salts, and the most widely-studied salt within this group is tetraammine Pt dichloride, (TPC), ($[Pt(NH_3)_4]Cl_2$)—a soluble ammine compound which has been used in autocatalyst manufacturing and plating applications. It is known that the ammine groups in TPC are very strongly bound (non-labile), making TPC a poor hapten. Furthermore, the chloride moiety is not directly coordinated to the central Pt atom (*i.e.*, it is ionic), in contrast to the chloride groups present in sensitising CHPS. The studies referenced in the following sections support the conclusion that TPC and other related tetraammines (*e.g.*, the dinitrate analogue) are likely devoid of respiratory sensitising potential.

HUMAN STUDIES

In the study by Linnett and Hughes (1999) on workers employed in three distinct and separate processes within a secondary refinery, chemical process operators (CPOs) exposed solely to TPC in an autocatalyst manufacturing plant showed no evidence of sensitisation. The same was not true of their counterparts in the refinery or laboratory where TPC was manufactured. The main differences between these groups of workers were that the latter workers were exposed to precursor CHPS in the production of TPC, whereas the autocatalyst production workers were exposed solely to TPC. And even though the autocatalyst production workers' exposures to soluble Pt were higher than those of workers in the refinery (see Table 6-1, page 9), the absence of diagnosed cases of PSS is compelling evidence that TPC was not a respiratory sensitiser. This was in good agreement with the study by Cleare *et al.* (1976) where workers with known sensitivity to hexachloroplatinate showed no evidence of elicitation reactions when challenged by skin prick tests involving TPC.

Lack of evidence for the sensitivity of TPC has also been confirmed in a prospective study of workers in a catalyst manufacturing plant in Australia (Steinfort *et al.*, 2008). No evidence of platinum sensitivity was seen in 71 workers exposed to TPC even though some of these workers were exposed to high concentrations of soluble platinum (10 to 20 µg soluble Pt/m^3).

NON-HUMAN TOXICOLOGY STUDIES AND MECHANISTIC INVESTIGATIONS

The above findings in human studies are also supported by the aforementioned studies in animals by Schuppe *et al.* (1997b) and Murdoch and Pepys (1984b, 1985). Whereas CHPS, and to a lesser extent cisplatin, showed evidence of sensitising effects in rodents, TPC clearly failed to do so in any of the immunological assays used to detect sensitisation.

6.2

PLATINUM SPECIES THAT ARE NOT RESPIRATORY SENSITISERS OR POSSESS UNCERTAIN SENSITISING POTENTIAL

BIOAVAILABLE PLATINUM SPECIES THAT HAVE FAILED TO INDUCE RESPIRATORY SENSITISATION

As described in Section 6.2, failure to induce respiratory sensitisation has largely been due to the lack of chemical reactivity and/or the low bioavailability of the platinum species in question. But certain forms of platinum which are bioavailable have failed to induce respiratory sensitisation. These include soluble platinum salts such as the nitrates in solution and sulphates.

Respiratory sensitisation reactions have not been definitely ascribed to these compounds in exposed workers, including large-scale applications such as use in catalyst systems. Moreover, at least for nitrate compounds in solution, this lack of evidence for respiratory sensitisation has been corroborated in a recent study on mice administered platinum nitrate through dermal exposures (Johnson Matthey, unpublished). The experimental design of the study was similar to that of Dearman *et al.* (1998) on CHPS and cisplatin. The study failed to show any evidence that platinum nitrate in solution was capable of producing the Th2-type cytokine release pattern typically associated with respiratory sensitisation. However, it did demonstrate induction of a Th1-type sensitisation response which has been shown to be characteristic of delayed contact hypersensitivity, *i.e.*, contact allergy (Kimber and Dearman, 2002; Kimber *et al.*, 2014). Chemicals that are skin irritants, including platinum nitrate salts (see Section 6.4), are likely to act along such pathways as well (Kimber *et al.*, 2002), and platinum nitrate in solution is markedly irritant.

PLATINUM SPECIES OF UNCERTAIN RESPIRATORY SENSITISATION POTENTIAL

The species covered under this section have uncertain respiratory sensitisation potential and include halogenated simple platinum salts such as platinum dichloride ($PtCl_2$) and platinum tetrachloride ($PtCl_4$).

HUMAN STUDIES

Workers potentially exposed to simple halogenated salts can be found in several industry sectors including catalyst production, surface plating, and in optical and glass applications. As is the case for other species believed to be non-sensitising, frank effects of sensitisation (in the absence of exposures to CHPS) have not been observed in these industry sectors.

NON-HUMAN TOXICOLOGY STUDIES AND MECHANISTIC INVESTIGATIONS

In in vitro studies on human peripheral blood mononuclear cells (PBMC), $PtCl_2$ enhanced the proliferation of PBMC and cytokine release of markers associated with Th2-type immune responses (Boscolo *et al.*, 2004). However, when tested in vivo, $PtCl_2$ failed to produce an immunologic reaction when injected into mice (Schuppe *et al.*, 1993). In contrast, $PtCl_4$ not only enhanced PBMC proliferation and the release of Th2-type cytokines in vitro (Di Gioacchino *et al.*, 2004) but also appeared to induce an immunologic reaction in the lymph nodes of mice when tested in vivo (Schuppe *et al.*, 1993). However, in the case of the latter study, the authors noted that upon further examination, it appeared that the lymph node reactions were likely caused by unspecified complexes that formed as a result of the instability of $PtCl_4$ in solution.

6.2 PLATINUM SPECIES THAT ARE NOT RESPIRATORY SENSITISERS OR POSSESS UNCERTAIN SENSITISING POTENTIAL

The overall evidence from these studies suggests that simple halogenated platinum salts do not directly induce immunologic responses in animal models when tested in vivo. These findings are in good agreement with the absence of frank effects of PSS in workers exposed to these salts. These studies also emphasise the need for caution when interpreting positive findings based solely on in vitro activity.

SUBSTANCE/GROUP	FORMULA	GROUP CHARACTERISTICS	RESPIRATORY SENSITISATION POTENTIAL
Elemental platinum	Pt	Low bioavailability. Low biological reactivity.	Not sensitising*
CHPS: Chloroplatinates Ammonium hexachloroplatinate Hexachloroplatinic acid Sodium hexachloroplatinate Potassium hexachloroplatinate Ammonium tetrachloroplatinate Sodium tetrachloroplatinate Potassium tetrachloroplatinate	 $(NH_4)_2PtCl_6$ H_2PtCl_6 Na_2PtCl_6 K_2PtCl_6 $(NH_4)_2PtCl_4$ Na_2PtCl_4 K_2PtCl_4	Halide ligand (chloride) coordinated to Pt. Labile leaving group (chloride). Known or predicted bioavailability.	Known sensitiser
Platins Cisplatin Carboplatin Oxaliplatin	 $[Pt(NH_3)_2Cl_2]$ $C_6H_{14}N_2O_4Pt$ $C_8H_{16}N_2O_4Pt$	Halide or other leaving group coordinated to Pt. Bioavailable.	Known sensitiser**
Tetraammine Pt salts Tetraammine Pt dichloride Tetraammine Pt diacetate Tetraammine Pt dinitrate Tetraammine Pt hydrogen carbonate	 $[Pt(NH_3)_4]Cl_2$ $[Pt(NH_3)_4](CH_3COO)_2$ $[Pt(NH_3)_4](NO_3)_2$ $[Pt(NH_3)_4](HCO_3)_2$	Ammine ligand which is poor leaving group. If present, chloride is ionic and not coordinated to Pt. Bioavailable.	Not sensitising*
Other Pt compounds (insoluble) Platinum oxide Platinum dioxide Platinum dichloride	 PtO PtO_2 $PtCl_2$	Low bioavailability. Low general biological reactivity.	Not sensitising*
Other Pt compounds (soluble) 'Platinum nitrate' Platinum sulphate Platinum tetrachloride‡	 Mixed Pt(IV) complex Mixed complex $PtCl_4$	Bioavailable.	Not sensitising***

* Supported by epidemiological evidence, mechanistic considerations and general industrial experience.
** Based on weight-of-evidence and mechanistic considerations, but potency may be less than CHPS.
*** Based on weight-of-evidence; see Sections 6.2.
‡ Only limited evidence of effect for this compound/testing affected by confounding (see also Table 6-3).

Table 6-2: Summary of the respiratory sensitisation potential of Pt substances

6.3

RESPIRATORY SENSITISATION: OBSERVATIONS ON MODE OF ACTION

Studies suggest that respiratory sensitisation to platinum species is primarily related to their chemical structure as opposed to only bioavailability dependence, though some intrinsic bioavailability is a requirement as defined by the Adverse Outcome Pathway for all respiratory sensitisers (North *et al.*, 2016). As previously described, certain soluble platinum compounds have shown little or no evidence of being sensitisers, whereas others have. Based upon the studies described above, as well as biochemical studies (Calvert *et al.*, 1993; Reedijk, 2003) and additional studies discussed below, a generalised theory has evolved which suggests that sensitisation is related to a platinum compound's ability to form reactive complexes with proteins.

With respect to CHPS, in order to induce an immune response, these low-molecular weight halogenated salts, must act as haptens—compounds which bind to larger molecules (often proteins), and in doing so, form antigens which are immunogenic. Without this ability to bind to a larger molecule (proteins), these compounds would be too small to be recognised as foreign by the immune system. In CHPS, the halogen moieties are present as weakly-bound ligands linked to a central metal atom, in this case Pt, to form a coordination complex. Because they are weakly-bound, these ligands ("leaving groups" in chemical parlance) can be readily displaced by sulphur- or nitrogen-containing ligands on proteins ("ligand exchange") to form adducts. Once ligand exchange occurs, the bulky Pt-protein complex formed becomes immunogenic. Studies suggest that highly chlorinated forms of halogenated salts (those with six to four chloride groups) may have a relatively higher potential to induce sensitisation than less chlorinated compounds, and that CHPS containing chlorine may be more sensitising than those containing other halogen groups (Cleare *et al.*, 1976; Cristaudo *et al.*, 2005).

However, as demonstrated by the non-halogenated platins such as carboplatin and oxaliplatin, there is no obligate requirement that the leaving group must be a halogen ligand directly coordinated to Pt in order to react with a protein to form an antigen. While platins are neutrally charged, their leaving groups—because they are weakly bound to Pt—can be replaced by water, yielding charged reactive intermediates. In turn, these intermediates ultimately form adducts with proteins.

In either case (CHPS or platins), once the platinum complex binds to a protein in forming an antigen the immune system mounts a response. Upon contact with an antigen, antibody molecules are synthesised. In the case of platinum-containing antigens, the antibody that is synthesised most often is immunoglobulin E (IgE). The induction and maintenance of platinum-related IgE antibody responses have been shown to be associated with Th2 helper cells (Dearman *et al.*, 1998; Ban *et al.*, 2010; Kimber *et al.*, 2014). Certain cytokines produced by these cells modulate eosinophil responses and the expression of IgE and the distal IgE-dependent cellular response. The IgE binds to receptor sites on mediator cells such as mast cells and basophils, resulting in the cellular release of histamine and other active amines from these cells upon re-exposure to the sensitising platinum compound. It is largely these degranulation products that produce the symptoms associated with PSS. As these responses tend to occur quickly after re-challenge with an antigen, they are characterised as Type I "immediate hypersensitivity

6.3 RESPIRATORY SENSITISATION: OBSERVATIONS ON MODE OF ACTION

reactions." Non-IgE mediated PSS, although much less frequent, may also occur; as evidenced by the fact that skin prick tests (SPT) may be negative in a minority of symptomatic workers (Calverley *et al.*, 1995; Chapter 7). Of the known sensitising platinum species, CHPS are considered to be more potent than platins and have been associated with the majority of occupational morbidity for this endpoint.

In the case of platinum species that have not been shown to be respiratory sensitisers (*e.g.*, elemental platinum or TPC), the complex series of reactions described above simply do not occur. The prevailing theory for their lack of respiratory sensitisation is predicated on the fact that these forms of platinum are too chemically inert, of insufficient bioavailability, or have ligands too firmly bound to the Pt atom to allow for the required ligand exchange with proteins necessary in the formation of immunogenic platinum antigens. And even in the case of platinum compounds that are bioavailable, it appears that some (*e.g.*, platinum nitrate salts in solution) may act through a different cellular pathway (Th1) associated with contact skin sensitisation, as opposed to the Th2 respiratory sensitisation pathway associated with both CHPS and platins. Although it is possible for some chemicals to cause either form of sensitisation, typically most chemical allergens do not act along both pathways (Kimber and Dearman, 2002; Lalko *et al.*, 2012; Kimber *et al.*, 2014). Supporting evidence for this can be seen in CHPS-exposed workers who clearly present with PSS but rarely show evidence of allergic contact dermatitis (see Section 6.4), suggesting that different platinum compounds may act through discrete sensitisation pathways (Kimber and Dearman, 2002; Lalko *et al.*, 2012; Baur, 2013; Kimber *et al.*, 2014).

It is worth noting that, in the acquisition of sensitisation to respiratory allergens—in addition to antigen formation—other molecular interactions may be operative (Kimber *et al.*, 2014). Of possible importance to platinum allergens is the presence and ability of certain factors, such as reactive oxygen species (ROS), to promote Th2 responses (Tang *et al.*, 2010). Lung irritants such as ozone and cigarette smoke are known ROS generators (Zuo *et al.*, 2013; Valavanidis *et al.*, 2013). As previously noted, these irritants have been shown to potentiate PSS in CHPS-exposed workers (Venables *et al.*, 1989; Calverley *et al.*, 1995; Niezborala and Garnier, 1996) and non-human primates (Biagini *et al.*, 1986). Thus, in addition to the antigen-formation capabilities of certain platinum compounds, other factors may play a role in the manifestation of platinum-associated respiratory sensitisation.

6.4

OTHER HEALTH EFFECTS OF PLATINUM AND ITS COMPOUNDS

OTHER HEALTH EFFECTS OF PLATINUM AND ITS COMPOUNDS

With the exception of studies of platins in patients and animal bioassays, long-term studies are sparse for most other platinum substances. Nevertheless, studies on endpoints other than sensitisation (*e.g.*, acute toxicity, irritancy, genotoxicity, reproductive toxicity screening and specific target organ toxicity) have been conducted across a number of platinum species. These are discussed below and summarised in Table 6-3. It is notable that, in general, compounds known to be respiratory sensitisers have also shown the greatest evidence of inducing other toxic effects, suggesting that sensitising species of platinum are typically more biologically reactive than other forms of platinum. The potentially serious toxicities other than sensitisation which are associated with platins should be noted.

ACUTE TOXICITY

Mortality due to acute exposures to platinum and its compounds has seldom been seen in humans. One report of death has been described in a 7-month old child accidentally administered 8g of potassium hexachloroplatinate (Hardman and Wright, 1896).

The lethal effects of several platinum compounds have been studied in animals via oral or parenteral administration, resulting in wide ranges of lethal doses (LD_{50}, the dose at which 50 percent of the animals die) depending on the route of exposure and the chemical structure of the compound tested (IPCS, 1991; Lewis, 1996). As a generality, the soluble compounds are more acutely toxic, but there is considerable overlap in the LD_{50} values across platinum species. Oral LD_{50} values (mg/kg body weight) in rats approximately range as follows: platins, 25-340 (the lowest dose being for cisplatin); CHPS, 25-200; soluble simple salts, 240-1000; insoluble simple salts, >2000->8000; tetraammine salts, >15,000 (IPCS, 1991). Although no oral LD_{50} value has been established for elemental platinum, oral doses of 25 mg/kg were not lethal in rats (Roshchin *et al.*, 1984, as cited in IPCS, 1991). Due to its inertness, elemental platinum would not be expected to be acutely toxic.

IRRITANT AND SKIN SENSITISATION EFFECTS

Dermal and eye irritancy have also been studied in animals across platinum species. There is no evidence in animals of skin irritation due to insoluble platinum compounds; no studies on eye irritation have been conducted on these compounds (IPCS, 1991). Most soluble species (including CHPS, platins, and other soluble compounds) have shown evidence of eye irritation in animals, with some compounds being severely irritating or even corrosive (IPCS, 1991). Skin irritation potential has shown wide variation, ranging from mild for certain soluble salts, *e.g.*, $PtCl_4$ (Campbell *et al.*, 1975) to severe or corrosive for others, *e.g.*, certain CHPS, platinum nitrate in solution (IPCS, 1991; Johnson Matthey, unpublished).

In assessing irritant and sensitisation effects in humans, it is important to take into consideration the differing mechanisms by which these effects manifest themselves. This is particularly important with

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respect to skin reactions, where the urticaria seen in CHPS-exposed workers and platin-infused patients is commonly believed to be IgE-mediated, whereas skin reactions due to primary irritant effects are not. There is, however, evidence that local irritation can augment cutaneous immunologic responses to chemical allergens and the acquisition of contact sensitisation by activation of dendritic cells and stimulation of inflammatory cytokines (Kligman, 1966; Kimber *et al.*, 2002). True allergic contact dermatitis has rarely been reported in workers exposed to platinum compounds (Hughes, 1980; Linnett, 1987). The irritant effects reported in Table 6-3, are representative of groups of platinum substances, based mainly on animal data.

Industrial experience suggests that soluble platinum salts, and in particular CHPS, can cause direct irritant effects to the respiratory tract by inhalation exposure. Symptoms include rhinitis, other local tissue reactions, coughing, difficulty breathing, and impaired respiratory function. Both exposures to particulates and to aerosolised solutions may cause these effects. As there are no fully validated animal tests that are available to predict respiratory tract irritancy, currently there is limited information on this toxicity endpoint.

GENOTOXICITY/ MUTAGENICITY

Platins have been shown to be mutagenic in several test systems and are acknowledged to represent a genotoxic risk (see also Section 6.4, 'Carcinogenicity'). They have been shown to be variously genotoxic and/or mutagenic—some markedly so—in a variety of in vitro and in vivo assays (IARC, 1987b; Gonzalez *et al.*, 1995; Sanderson *et al.*, 1996; Gebel *et al.*, 1997; Vijayalaxmi and Prem D'Souza, 2004; Silva *et al.*, 2005; Brozovic *et al.*, 2011; Dertinger *et al.*, 2014). Evidence of genotoxic effects has been demonstrated in health care workers exposed to anticancer drugs (NIOSH, 2004), but direct correlations with specific drugs within the platin series have not been well established (Hewitt, 1997).

Several other groups of soluble Pt compounds, including Pt^{2+} and Pt^{4+} forms and encompassing anionic as well as cationic compounds have given positive responses in bacterial reverse mutation assays (Ames test), but they do not exhibit the level of potency evident with the platins. Certain of these substances also induced gene mutations and micronuclei in mammalian cells in vitro, suggestive of clastogenic (and possibly also aneugenic) activity. However, in nearly all cases no robust in vivo assay data are available with which to make a firm judgement on genotoxicity/ mutagenicity. In the case of insoluble Pt compounds such as $PtCl_2$, the in vitro data are more conflicting including both negative and positive test results (Gebel *et al.*, 1997; U.S. EPA, 1979; Migliore *et al.*, 2002). In line with various worldwide expert guidelines, caution is advised in making predictions of in vivo genetic toxicity based only on in vitro activity.

CARCINOGENICITY

No data exist for carcinogenicity with the exception of the platins. Human epidemiology studies of secondary malignancies potentially caused by platins are confounded by the fact that platins are usually administered in combination with other genotoxic drugs or radiation. However, based upon the presence of cisplatin-induced DNA adducts in patients receiving cisplatin chemotherapy (Reed *et al.*, 1993) and tumours in animals administered cisplatin through intraperitoneal injection (Leopold *et al.*, 1979; Satoh *et al.*, 1993; Waalkes *et al.*, 2006), the International Agency for Research on Cancer has categorised cisplatin as Group 2A, "probably carcinogenic to humans" (IARC, 1987a). Likewise, the U.S. National Toxicology Programme has listed cisplatin as

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OTHER HEALTH EFFECTS OF PLATINUM AND ITS COMPOUNDS

"reasonably anticipated to be a human carcinogen" (NTP, 2011). Lifetime cancer risks for cisplatin have been estimated by the Dutch Expert Committee on Occupational Standards of the Health Council of the Netherlands (HCN, 2005). There are grounds to suspect that other platins may also pose a carcinogenic hazard, though this has not been definitively established.

TARGET ORGAN TOXICITY

As noted in Section 6.2, due to the high doses of platins required to treat cancer patients, serious side effects in various organs have often been observed (McKeage, 1995). Exposures to cisplatin are primarily associated with nephrotoxicity, neurotoxicity, and ototoxicity, whereas myelotoxicity is predominant for carboplatin, and neurotoxicity is predominant for oxaliplatin (Screnci and McKeage, 1999; Arany and Safurstein, 2003; Hartmann and Lipp, 2003). Renal toxicity may be of particular importance due to the fact that the tissue distribution pattern for most platinum species involves accumulation in the kidneys (see Chapter 5 on Toxicokinetics). Although renal toxicity has not been associated with occupational exposures to other platinum species, there is some evidence in animals, *e.g.*, the kidney was confirmed as the most significant target organ in a 28-day oral repeat dose study in the rat with ammonium hexachloroplatinate (EPMF, unpublished data 2015). Histopathological lesions included hyaline casts; lymphocytic infiltration and fibrosis; tubular basophilia and dilation; and tubular necrosis.

REPRODUCTIVE AND/OR DEVELOPMENTAL EFFECTS

All the platins have shown evidence of reproductive/developmental effects in animals including fetotoxicity, teratogenicity, and sperm abnormalities (Lazar *et al.*, 1978; Sorsa *et al.*, 1985; Koc *et al.*, 1994; Vijayalaxmi and Prem D'Souza, 2004; Health Canada, 2009), and are classified as reproductive toxicants. With respect to other platinum species, test data are limited and earlier studies do not conform to current guidelines. No fetotoxic effects were seen in rat dams administered platinum metal, $PtCl_2$, or $PtCl_4$ in their diet (Bogenrieder *et al.*, 1992; Kirchgessner and Reichlmayr-Lais, 1992), but when $Pt(SO_4)_2$ was administered to gestating female mice (200 mg Pt/kg body weight on pregnancy day 7 or 12) it caused a reduction in pup weights (D'Agostino *et al.*, 1984). The tetrachloroplatinate salt Na_2PtCl_4 also caused a reduction in the weights of mice pups (D'Agostino *et al.*, 1984). Fetotoxicity was also evident in a recent screening study in rats (EPMF, unpublished results) with a hexachloroplatinate salt (NH_4PtCl_6), though overt developmental toxicity or effects on fertility were not evident at up to 100 mg/kg/d. Developmental toxicity (pre- and post-natal) was detected in a screening study with a Pt-siloxane compound (Karstedt Catalyst) at a relatively high dose level of 500 mg/kg/d.

6.4

TABLE 6-3: SUMMARY OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURES TO PLATINUM AND PLATINUM COMPOUNDS

SUBSTANCE CATEGORY EXAMPLE SUBSTANCES	ACUTE TOXICITY			CORROSIVITY AND IRRITANCY		SENSITI-SATION		GENOTOXIC/ MUTAGENIC EFFECTS	CANCER EFFECTS	TARGET ORGAN EFFECTS	REPRODUCTIVE/ DEVELOPMENTAL EFFECTS	COMMENTS
	H	M	L	Eye	Skin	Resp	Skin	In Vitro				
Elemental Platinum and Alloys: Platinum black/ sponge, powder etc.			ND [1]	ND [2]	ND [1]	○ [3]	ND [1]	ND [4]	ND	ND [1]	○ [5]	[1] Activity not expected; [2] Expected to be a mechanical irritant only; [3] Based on human evidence; [4] Massive Pt forms; [5] Activity not predicted., based on limited animal data and inertness.
CHPS: Chloroplatinic acid, Ammonium hexachloroplatinate, Sodium tetrachloroplatinate etc.	◖ [1]	●		● [2]	● [3]	● [4]	● [5]	●	ND	● [6]	○ [7]	[1] Applies only to Na_2PtCl_4; [2] Typically irritating to corrosive; [3] Mildly irritating to corrosive; [4] Potent human; [5] Based mainly on urticaria in workers; [6] Kidney; [7] Developmental effects absent.
Platins: Cisplatin, Carboplatin, Oxaliplatin	◖ [1]	◖ [1]		● [2]	● [2]	●	● [3]	● [4]	◖ [5]	● [6]	● [7]	[1] Cisplatin acute oral toxicity is 'H'., all others "M"; [2] Moderate to severe irritant; [3] Based mainly on non-contact urticaria in patients; [4] Effects in vivo also shown; [5] Firmest evidence is for cisplatin; [6] Target organs: multiple - includes kidney, nervous, immune, and blood systems; [7] Fertility, fetotoxic, and developmental effects.

● Known effect

◖ Known effect/restricted to some substances in category

○ Data available: effect absent or limited

* Data available: effect uncertain, conflicting or inconclusive

ND No data available

Acute toxicity: High (H) = GHS (Globally Harmonized System) Category 1 or 2 | Moderate (M) = GHS Category 3 or 4 | Low (L) = GHS Category 5 or unclassified | Values for oral route unless stated.
Category 1: $LD_{50} \leq 5$ mg/kg
Category 2: $LD_{50} > 5$ mg/kg and < 50 mg/kg
Category 3: $LD_{50} \geq 50$ mg/kg and < 300 mg/kg
Category 4: $LD_{50} \geq 300$ mg/kg and < 2000 mg/kg
Category 5: $LD_{50} \geq 2000$ mg/kg

6.4

TABLE 6-3: SUMMARY OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURES TO PLATINUM AND PLATINUM COMPOUNDS

SUBSTANCE CATEGORY EXAMPLE SUBSTANCES	**ACUTE TOXICITY**			**CORROSIVITY AND IRRITANCY**		**SENSITI-SATION**		**GENOTOXIC/ MUTAGENIC EFFECTS**	**CANCER EFFECTS**	**TARGET ORGAN EFFECTS**	**REPRODUCTIVE/ DEVELOPMENTAL EFFECTS**	**COMMENTS**
	H	**M**	**L**	**Eye**	**Skin**	**Resp**	**Skin**	**In Vitro**				
Insoluble simple compounds/salts: Platinum dioxide, Platinum dichloride, etc.			●	ND [1]	○	○	○	*	ND	ND [1]	○ [2]	[1] Activity not expected; [2] Activity not predicted based on limited animal data and low bioavailability.
Soluble salts: Platinum nitrate, Platinum sulphate, Platinum tetrachloride, Hydrogen hexa-hydroxyplatinate etc.		●		●	● [1]	○ * [2]	* [3]	●	ND	* [4]	* [5]	[1] Corrosive, nitrates in solution only, due to low pH/high acid reserve; others typically moderate; [2] Limited evidence for $PtCl_4$/ unstable in solution; [3] Pt nitrate; [4] Activity possible, kidney; [5] Very limited evidence of effects.
Tetraammine Platinum Salts: Acetate, Chloride, Hydrogen carbonate, Nitrate salts etc.			●	●	● [1]	○	○	● [2]	ND	○	ND	[1] Moderately irritating; [2] Bacterial reverse mutation and mammalian cell assays (positive in vivo tests are currently lacking).

● Known effect

◖ Known effect/restricted to some substances in category

○ Data available: effect absent or limited

* Data available: effect uncertain, conflicting or inconclusive

ND No data available

Acute toxicity: High (H) = GHS (Globally Harmonized System) Category 1 or 2 | Moderate (M) = GHS Category 3 or 4 | Low (L) = GHS Category 5 or unclassified | Values for oral route unless stated.
Category 1: $LD_{50} \leq 5$ mg/kg
Category 2: $LD_{50} > 5$ mg/kg and < 50 mg/kg
Category 3: $LD_{50} \geq 50$ mg/kg and < 300 mg/kg
Category 4: $LD_{50} \geq 300$ mg/kg and < 2000 mg/kg
Category 5: $LD_{50} \geq 2000$ mg/kg

6.5

TOXICITY OF OTHER PLATINUM GROUP METALS (PGMs) AND THEIR COMPOUNDS

TOXICITY OF OTHER PLATINUM GROUP METALS (PGMs) AND THEIR COMPOUNDS

This section provides an abbreviated toxicology overview covering the other PGMs (viz. palladium, rhodium, iridium, ruthenium and osmium) and their industrially important compounds. Emphasis is given to those effects of relevance to occupational contexts. Information drawn from reviews of PGM toxicology, such as IPCS, 2002; HCN, 2002; DFG 2006; and DFG, 2007, has been augmented and updated via datasets emerging from recent toxicity testing, *e.g.*, studies performed for EU REACH Regulation registrations. As these newer data become incorporated in REACH substance registration dossiers, further specifics will be publically available via the European Chemicals Agency (ECHA) website. Due to space constraints, most of the available information is summarised via Table 6-4, which provides toxicity endpoint data for major categories of PGM substances. Information on more specialised organo-PGM complexes, *e.g.*, those designed for catalytic or therapeutic applications, is not addressed in this chapter. It should be borne in mind that the occupational health database for other PGMs, particularly with low production volumes, can be sparser than that available for platinum and its compounds.

Unlike complex halogenated platinum salts (CHPS) and the platins, the evidence for respiratory sensitisation due to industrial exposures to non-platinum PGMs is not compelling. In a few instances, positive SPT to salts of palladium, rhodium, iridium, or ruthenium have been recorded in workers with significant co-exposure to CHPS (Murdoch *et al.*, 1986; Murdoch and Pepys, 1987; Santucci *et al.*, 2000; Cristaudo *et al.*, 2005). The responses, often seen in conjunction with a positive SPT to CHPS, are most likely attributable to cross-sensitisation reactions to CHPS, or are otherwise complicated by uncertainties over delineation of the causative agent. Much rarer case reports exist of symptomatic respiratory sensitisation reactions in workers whose exposures were predominantly to PGM salts other than platinum: viz., salts of iridium (Bergman *et al.*, 1995), palladium (Daenen *et al.*, 1999), and rhodium (Merget *et al.*, 2010). These workers had no known or limited exposures to platinum salts, and negative—or only weakly positive—SPT responses to CHPS. In each instance, the subjects presented with a variety of symptoms including rhinitis, dyspnoea, asthma, and urticaria. The causal basis of these three cases remains unclear (possibly representing extremes of individual susceptibility), but industrial experience strongly supports a conclusion that non-platinum PGM substances are not common workplace respiratory sensitisers.

With the exception of osmium and ruthenium tetroxides, which exhibit high acute toxicity via the oral and inhalation routes in experimental animals, the majority of non-platinum PGM substances possess only low to moderate acute toxicity (Table 6-4). Studies in animals and human experience have demonstrated the very high tissue reactivity of osmium and ruthenium tetroxides—they are extremely irritant to the respiratory tract, may cause pulmonary oedema with higher exposures, and are also corrosive to the eyes and skin (Léonard 1988a; 1988b). Table 6-4 summarises the local eye and skin effects for other PGM substance categories, which are typified by a spectrum of low to moderate contact irritancy except for the corrosivity evident for compounds possessing a very low pH, such as the PGM nitrates.

As a class property, it is evident that soluble Pd^{2+} ion is a moderately potent contact sensitiser based

6.5 TOXICITY OF OTHER PLATINUM GROUP METALS (PGMs) AND THEIR COMPOUNDS

on tests for delayed contact hypersensitivity in animals and from human case reports (see in particular IPCS [2002]). Hypersensitivity reactions have even been observed in humans exposed to low solubility Pd forms, including alloys (although this has most often been described in the case of protracted oral contact with Pd-containing dental restorations). However, allergic contact dermatitis induced by palladium in occupational settings remains rarer than might be expected from the animal study outcomes and the incidence of palladium hypersensitivity observed in dermatology clinics. A complicating factor in discriminating Pd-induced contact allergy (Pd mono-sensitisation) is that of multi-metallic reactivity, especially to nickel. Hence palladium allergy is nearly always observed together with nickel allergy: a median prevalence was reported in one European study of 7-8% (Faurschou *et al.*, 2011), whereas the same researchers reported the median prevalence of palladium mono-sensitisation, *i.e.*, presence of palladium allergy and the absence of nickel allergy, as 0.2% (range 0–1.6%) in dermatitis patients, and 0.5% (range 0–7.2%) in dental patients. Based on current knowledge, subpopulations at particular risk of dermal reactions to palladium include people with existing delayed contact hypersensitivity to nickel. Some rhodium(I) and rhodium(III) compounds have tested positive in assays for delayed contact hypersensitivity potential (see Table 6-4) and occasional human case reports do exist (*e.g.*, Goosens *et al.*, 2011).

Although there have been occasional reports of target organ or reproductive toxicity in animal studies, evidence from recent test guideline/Good Laboratory Practice conformant repeat dose toxicity studies in rodent suggests that even bioavailable non-platinum PGM compounds possess limited systemic toxicity at doses relevant to occupational contexts (see Table 6-4). It should be noted that some data limitations do exist, *e.g.*, in relation to repeat dose inhalation toxicology, and the dataset on iridium substances is currently sparse.

There is no human evidence for the carcinogenicity of non-platinum elemental PGMs or their salts. The only available carcinogenicity studies on palladium(II) chloride and also rhodium(III) chloride in mice cannot be evaluated due to some technical deficiencies (Schroeder and Mitchener (1971); DFG, 2006; DFG, 2007). Rhodium(III) compounds have been shown to be genotoxic in short-term in vitro and in vivo tests, including consistent positive results for various soluble rhodium(III) compounds in bacterial mutagenicity tests (HCN, 2002; DFG, 2007; Table 6-4). HCN (2002) has recommended classifying water-soluble $RhCl_3$ and all other rhodium compounds that generate rhodium(III) ions in solution as suspected carcinogens, but long-term carcinogenicity data in support of such a conclusion are currently not available. Short-term genotoxicity assays on other non-platinum PGMs have typically provided negative results.

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TABLE 6-4: SUMMARY OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURES TO OTHER PLATINUM GROUP METALS AND THEIR COMPOUNDS

SUBSTANCE CATEGORY EXAMPLE SUBSTANCES	ACUTE TOXICITY			CORROSIVITY AND IRRITANCY		SENSITI-SATION		GENOTOXIC/ MUTAGENIC EFFECTS	CANCER EFFECTS	TARGET ORGAN EFFECTS	REPRODUCTIVE/ DEVELOPMENTAL EFFECTS	COMMENTS
	H	M	L	Eye	Skin	Resp	Skin	In Vitro				
Elemental PGMs and Alloys: Pd, Rh, Ru, Ir, Os including sponge and powder forms, alloys.			ND [1]	ND [2]	ND [1]	○ [3]	○ [4] ◖ [5]	ND	ND	ND [4] ✻ [6]	○ [7]	[1] Activity not expected; [2] Expected to be a mechanical irritant only; [3] Based on weight of human evidence; [4] Except Pd; [5] Some human case reports for metallic Pd; [6] Data for Pd inconclusive; [7] Activity not predicted, based on limited animal data and inertness.
Insoluble simple compounds/salts: PdO, Rh_2O_3, RuO_2, IrO2; hydroxides of Pd, Rh, Ru or Ir; sulphides of Pd, Ru or Ir etc.			●	ND [1]	○ [2]	○ [3]	○ [4]	○	ND	ND [5]	○ [5]	[1] Activity not expected; [2] From PdO and RuO_2 data and bioavailability inferences; [3] Based on weight of human evidence; [4] Limited activity possible for insoluble compounds; [5] Activity not predicted based on animal data/low bioavailability.
Tetroxides: OsO_4 and RuO_4.	● [1]			● [2]	● [2]	ND	ND	● [3]	ND	● [4]	✻ [3]	[1] Inhalation and oral routes; [2] Corrosive, also severe respiratory irritant; [3] OsO_4; [4] Multiple, including respiratory system, eye, liver, kidney.

● Known effect

◖ Known effect/restricted to some substances in category

○ Data available: effect absent or limited

✻ Data available: effect uncertain, conflicting or inconclusive

ND No data available

Acute toxicity: High (H) = GHS (Globally Harmonized System) Category 1 or 2 | Moderate (M) = GHS Category 3 or 4 | Low (L) = GHS Category 1 | $LD_{50} \leq 5$ mg/kg
Category 2: $LD_{50} > 5$ mg/kg and < 50 mg/kg
Category 3: $LD_{50} \geq 50$ mg/kg and < 300 mg/kg
Category 4: $LD_{50} \geq 300$ mg/kg and < 2000 mg/kg
Category 5: $LD_{50} \geq 2000$ mg/kg

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	H	M	L	Eye	Skin	Resp	Skin	In Vitro				
Soluble Pd salts: $PdCl_2$, $PdSO_4$, $Pd(NO_3)_2$, Pd acetate, Tetra- and Hexachlororhodates.		●		●	◖ [1]	○ [3]	● [2]	○	ND	○ [4]	○ [4]	[1] Low pH substances corrosive, others range from non-irritant to moderately irritant; [2] Based on human and animal data; [3] Based on weight of human evidence; [4] Dataset limited/ based on chloropalladates.
Ammine Pd compounds: Tetraammine Pd salts (Chloride, Hydrogen carbonate, Acetate, Nitrate etc); Diammine-dichloropalladium (DDP).		●		● [1]	○	○ [2]	◖ [3]	○	ND	○ [4]	○	[1] DDP causes irreversible damage, tetraammine compounds are irritant; [2] Based on human evidence; [3] Tetraammine Pd compounds but not DDP; [4] Limited GI tract effects.
Soluble Rh(III) compounds: Sulphate, Chloride, Nitrate, Acetate, Iodide, Hexachlororhodates.		●	● [1]	●	◖ [2]	○ [3]	◖ [4]	●	ND	○	○ [5]	[1] Hexachlororhodates; [2] Low pH substances corrosive, others non-irritant; [3] Based on human evidence; [4] Rh nitrate; [5] Dataset is limited.
Dicarbonylacetyl-acetonatoRh(I)		●		●	○	○	●	ND	ND	ND	ND	Substance also known as Rh50.

● Known effect

◖ Known effect/restricted to some substances in category

○ Data available: effect absent or limited

∗ Data available: effect uncertain, conflicting or inconclusive

ND No data available

Acute toxicity: High (H) = GHS (Globally Harmonized System) Category 1 or 2 | Moderate (M) = GHS Category 3 or 4 | Low (L) = GHS Category 1 | $LD_{50} \leq 5$ mg/kg
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	H	**M**	**L**	**Eye**	**Skin**	**Resp**	**Skin**	**In Vitro**				
Soluble Ru(III) compounds: Chloride, Acetate etc.		●	● [1]	●	◖ [2]	○ [3]	○	*	ND	*	ND	[1] Acetate; [2] Low pH substances corrosive, others non-irritant; [3] Based on weight of human evidence.
Chloro-Ir compounds (hydrates): Trichloride, Tetrachloride, Hexachloroiridates.		●		●	●	○ [1]	○	*	ND	* [2]	ND	[1] Isolated human case report for hexachloroiridates (considered as only limited evidence of effect); [2] Renal and immune system effects have been reported (non-GLP study requiring confirmation) [GLP = good laboratory practice].

● Known effect

◖ Known effect/restricted to some substances in category

○ Data available: effect absent or limited

* Data available: effect uncertain, conflicting or inconclusive

ND No data available

Acute toxicity: High (H) = GHS (Globally Harmonized System) Category 1 or 2 | Moderate (M) = GHS Category 3 or 4 | Low (L) = GHS Category 1 | $LD_{50} \leq 5$ mg/kg
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