IPA

INTERNATIONAL PLATINUM GROUP METALS ASSOCIATION

5

TOXICOKINETICS OF PLATINUM AND OTHER PLATINUM GROUP METALS

CONTENTS

SUMMARY

- Toxicokinetics (TK) describes how the body absorbs, distributes, transforms and excretes a chemical substance. Limited data exist on the toxicokinetics of PGMs; most of what is known is based upon studies in animals.

- Absorption, distribution, and excretion of PGMs can be shaped by factors including chemical/physical characteristics, concentration, particle size, water solubility, and exposure route. Such parameters may impact on absorption, subsequent systemic 'bioavailability,' and potential toxicity. However, in some cases chemical transformation events—particularly for coordination complexes of Pt—can have a more significant role in toxicity (see Chapter 6).

- Data suggest that soluble PGM forms are more likely to be absorbed than insoluble forms and are thus somewhat more bioavailable, regardless of the route of exposure. Insoluble or poorly soluble PGMs are not readily absorbed. After ingestion of low solubility forms (or following respiratory tract deposition and mucociliary clearance into the gut) most of the dose is voided directly from the gastrointestinal tract. Dermal absorption has been demonstrated for certain soluble PGM compounds including chloroplatinates.

- Distribution of bioavailable PGM forms has been shown in animals to be mainly to the kidney, with lesser amounts to other tissues, including the liver, spleen, adrenal glands, other soft tissues and bone.

- Although the simple inorganic PGM compounds do not undergo metabolism, they may be subject to various transformations in biological milieu including hydrolysis, ligand exchange, and oxidation state changes. In some instances, there is potential for binding to macromolecules including proteins and nucleic acids.

SUMMARY

- Elimination of insoluble or sparingly soluble forms of PGMs which are inhaled (or directly ingested) is mainly by mucociliary clearance to the intestinal tract and excretion in the faeces. Based on human data, excretion of soluble Pt salts appears to be biphasic, with a renal excretion component also evident. Urinary excretion can also occur for other soluble PGM compounds.

- Biological monitoring studies in PGM workers have shown blood, serum, and urinary Pt levels considerably higher than those in the general population. Pt concentrations in biological fluids appear to rise with increasing workplace exposure and so represent a useful marker for exposure. However, no robust relationship has been established between biomonitored levels and the development of platinum salt sensitivity (PSS).

- Toxicokinetics data on anticancer Pt drugs (platins) have been mainly derived from intravenous administration which is of limited relevance to occupational settings. When injected, they are rapidly distributed to many tissues and undergo transformation to biologically active species. Renal excretion predominates. Biological monitoring of Pt levels (blood or urine) is a useful occupational exposure monitor for healthcare workers handling platins, as it is sensitive and because it integrates absorption from all routes.

5.1

OVERVIEW OF THE TOXICOKINETICS OF PGMs

This chapter focuses on the mammalian toxicokinetics (TK) of platinum and its compounds, while also incorporating a brief section covering other industrially important PGMs. In addressing the TK profile of Pt, the main sections deal in turn with the absorption, distribution, transformation and excretion of simple Pt forms including inorganic salts. Due to the different context of the TK dataset for Pt anticancer drugs (platins), mainly derived from intravenous administration during drug therapy, these compounds are covered in a separate section (5.7).

The non-pharmacological compound TK dataset on Pt, and other PGMs, is only partially complete and data gaps exist. Most information is available for Pt substances, which can be considered to group either into water-soluble Pt compounds [principally simple salts such as $Pt(SO_4)_2$ and $PtCl_4$ or complex halogenated salts such as $(NH_4)_2PtCl_6$ and K_2PtCl_4], or into insoluble forms [Pt metal, Pt-based alloys, PtO_2, and $PtCl_2$]. A reasonably comprehensive human biomonitoring dataset has also been established (see Section 5.6).

As this guidance is intended to be relevant to occupational contexts, emphasis is placed on TK related to the inhalation and dermal exposure routes, but it should be borne in mind that translocation of inhaled material to the gastrointestinal (GI) tract is particularly relevant for metals, following particle-size dependent deposition in the upper respiratory tract. Hence systemic availability of metals, including PGMs, can be influenced by GI uptake of translocated material, and also by incidental oral exposure, *e.g.*, hand-to-mouth transfer (ICMM, 2006). Specific data on local respiratory tract TK behaviour is very limited.

Absorption, distribution and excretion of Pt and other PGMs can be shaped by factors including chemical and physical characteristics (such as water solubility), concentration, particle size, and exposure route. Such parameters impact on absorption, subsequent systemic and local tissue "bioavailability", and ultimately on toxicity. However, the structural configuration of a Pt species, particularly for coordination complexes, also has a major bearing on toxicity. Hence not all soluble Pt compounds have been shown to be biologically reactive or significantly toxic (refer to Chapter 6 on Toxicity). Conversely, the therapeutically important 'platin' chemotherapy drugs cisplatin, carboplatin and oxaliplatin have relatively low water solubility (ranging from 0.25 – 1.4 g/100 ml at 20°C), resulting in generally poor oral bioavailability, but they all have significant biological activity and systemic toxicity due to their reactive nature toward biomolecules—properties which are dependent on the leaving group behaviour of these Pt complexes.

A number of investigations have been performed on the bioaccessibility of Pt and other PGMs in urban aerosol particulates (often in relation to autocatalyst emissions). These have utilised model systems reliant on physiologically-based extractants such as simulated gastric fluid and lung fluids (Wiseman and Zereini, 2009; Wiseman, 2015a) to estimate the amount of PGM that becomes dissolved and thus available for potential absorption.

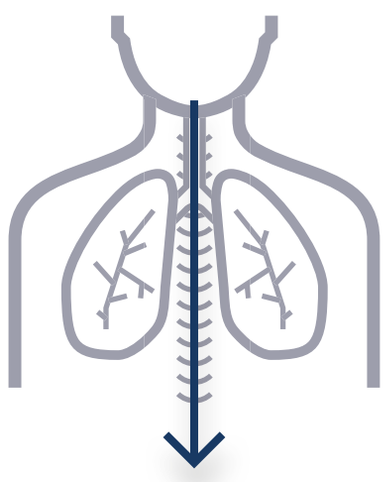
Caution is required in simply extrapolating the outcome of such studies to conclusions on PGM bioavailability and predicted absorption characteristics, as they can be affected by interpretative

5.1 OVERVIEW OF THE TOXICOKINETICS OF PGMs

and methodological limitations. This includes an assumption that surrogate physiological extractant bioelution in such systems directly represents actual bioavailability following absorption in vivo. However, the bioavailability behaviour of metal species in biological systems is considerably more complex (*e.g.*, see Mukhtar and Limbeck, 2013). In addition, some previous studies have likely overestimated bioavailability due to their dependence on 0.2 µm filtration during post-extractant separations which have failed to properly distinguish between truly soluble (*i.e.*, dissolved) PGM moieties versus ultrafine PGM particulate. Newer studies have properly differentiated between such entities. Other methodological issues include the use of inappropriate sample: extractant loading ratios (variance in bioelution methodologies has been reviewed by Wiseman, 2015b).

As with other TK assessments of metal-containing substances, analysis for a specific PGM analyte as the metal is used as a marker (in studies of absorption, distribution and excretion) even though the actual exposure may be to a PGM compound or ionic form.

Due to the currently limited industrial production of nanoforms of PGMs, they are not covered in this chapter.



5.2

ABSORPTION

Inhalation and oral absorption of Pt metal and low solubility Pt compounds appears to be very low (typically less than 1%). Water-soluble compounds are absorbed to a somewhat higher extent. Full quantitation of the amounts and rates of absorption of inhaled Pt compounds (and other PGMs) in humans is currently lacking, and as previously discussed, extrapolation of systemic bioavailability from older bioaccessibility models using surrogate lung and gastrointestinal fluids can be misleading.

INHALATION

HUMAN STUDIES

When two volunteers inhaled ammonium hexachloroplatinate at calculated mean air concentrations of 1.7 and 0.15 µg/m³, respectively, absorption of this water-soluble compound appeared to be rapid with urinary Pt concentrations peaking approximately 10 hours later (Schierl *et al.*, 1998). However, this study gives little quantitative insight into the extent of absorption versus the total inhaled dose. End-of-workshift elimination kinetics in occupational cohorts exposed to soluble tetrachloroplatinate and platinum nitrate salts, confirmed that rather rapid absorption took place (Schierl *et al.* 1998; 1999), but again do not define uptake metrics related to the proportion of the inhaled dose.

By analogy with other metals and their compounds, systemic absorption of inhaled aerosols of Pt compounds deposited in the respiratory tract are expected to be influenced by a size-dependent pattern of regional deposition within the respiratory tract, together with local bioavailability. General population TK based on low dietary intakes are of limited relevance to respiratory tract mucociliary clearance into the gut occurring in occupational contexts, but from an estimated intake of about 20 ng Pt/kg-bw/day via the diet it has been calculated that 42–60% of dietary Pt undergoes absorption (Vaughan and Florence, 1992). This is much higher than the total absorption values derived from animal studies (see below). The disparity may be due to the inherent imprecision in such estimates, or to differences in bioavailability of dietary forms.

OTHER DATA

The following studies in animals have shown patterns of absorption of inhaled Pt aerosols typical of mucociliary clearance of particles from the respiratory tract, combined with some absorption from particles deposited in the deeper regions of the respiratory tract:

- In acute inhalation studies on rats exposed to particles [diameter around 1 µm] of radiolabelled Pt, PtO_2, $PtCl_4$ or $Pt(SO_4)_2$, the appearance of most of the radiolabel in rat faeces indicates that systemic Pt absorption was low (Moore *et al.*, 1975a).
- An acute study where powdered Pt (particle diameter 0.2-0.8 µm) was administered to rats by intratracheal instillation led the investigators to calculate that only around 0.8% of the Pt dose was bioavailable, based on the Pt content of the urine and tissues other than the lungs (Artelt *et al.*, 1999).
- After inhalation by rats of aluminium oxide particles coated with elemental Pt (to simulate vehicle emission catalyst converter particulate) for 90 days, only 2% of the dose was found in the lungs, urine and other tissues.

5.2

ABSORPTION

Of the Pt deposited in the lungs, about 20-30% was estimated to be bioavailable (*i.e.* about 0.4-0.6% of total dose). The coated particle diameter was around 1.3 µm with associated nanoscale Pt.

- In rats administered the same particles via intratracheal instillation, the bioavailability of the lung Pt retained after 90 days was estimated to be somewhat lower (around 8-14%).
- A study in the rat (Oberdörster *et al.*, 2000) based on examination of only one animal 0.5 hours after a 6-hour inhalation exposure to ultrafine Pt particles (~0.01 µm diameter), nearly all Pt remained in the lung with minimal systemic absorption evident (<1%).

DERMAL

Little objective data currently exist on the percutaneous absorption of Pt and its compounds. By analogy with similar metals, elemental Pt and lower solubility compounds probably undergo very limited dermal absorption. Human in vitro skin permeation studies on the readily soluble Pt compound potassium tetrachloroplatinate using full thickness skin from African and Caucasian donors showed mean permeation values of 4.8 and 2.3%, respectively, after 24 hours (Franken *et al.*, 2015), though values for a duration equivalent to typical workshift-length (8 hours) were about 80% lower. Nevertheless, these experiments indicate that such compounds can penetrate human skin to an extent relevant to considerations of toxicities such as allergenicity.

ORAL

Absorption of insoluble Pt species administered orally in laboratory animals is low. Only 0.11% of Pt was absorbed following gavage administration of Pt-coated alumina particles to rats (Artelt *et al.*, 1999). When rats were administered PtO_2 in the diet, very little Pt was found in any organs (US EPA, 1977).

Absorption of soluble Pt compounds has been reported to be very low. In rats, less than 1% of an oral dose of radiolabelled $PtCl_4$ was absorbed (Moore *et al.*, 1975b,c). Similar results were obtained when $Pt(SO_4)_2$ was administered orally to mice (Lown *et al.*, 1980). In studies where comparisons were possible, oral administration of soluble salts resulted in slightly higher Pt concentrations in blood and tissues, compared with insoluble salts (Reichlmayr-Lais *et al.*, 1992; US EPA, 1977).

5.3

DISTRIBUTION

In the case of the more bioavailable forms of Pt, the typically small proportion (<2%) which is absorbed distributes mainly to the kidney, with lesser amounts to other tissues, including the liver, spleen, adrenal glands, other soft tissues and bone. Intra-tissue and intracellular dispositions of insoluble and soluble Pt forms are currently largely unknown.

HUMAN STUDIES

Few relevant data exist for organ and tissue distribution in humans. Historically, Pt levels in humans not occupationally exposed to platinum compounds has been shown to vary very widely with reported values ranging from <1 to about 4000 ng/g wet tissue including liver, kidney, lung, heart, and muscle (Johnson *et al.*, 1976; SCOEL, 2011). See also Section 5.6 (Biological Monitoring).

OTHER DATA

After short-term inhalation (48-minute) exposures of rats, using particulates with aerodynamic diameters approximating to 1 µm of insoluble [Pt, PtO_2] and [$PtCl_4$, $Pt(SO_4)_2$] Pt forms, measured radiolabel concentrations were highest in the respiratory tract deposition sites of the lungs and trachea, followed by the kidneys and bone, with lower levels in other soft tissues (Moore *et al.*, 1975a). Following intratracheal instillation of Pt particulate (0.2 to 0.8 µm diameter), Pt concentrations 90 days later were highest in the lungs, with lower concentrations in the kidneys (Artelt *et al.*, 1999). In longer term inhalation experiments with inhaled Pt-alumina particles (90-day exposure), a total of 2% of dose was found in the lungs, urine, kidneys, liver, other organs, and bones.

With oral administration of various insoluble Pt species, the highest concentrations were found in the kidneys, with other organs containing lesser or negligible amounts (Artelt *et al.*, 1999; Reichlmayr-Lais *et al.*, 1992; US EPA, 1977). Quite similar findings in rodents involving distribution to the kidneys and liver were reported by Moore *et al.*, 1975b and Lown *et al.*, 1980 using soluble forms ($PtCl_4$ and $Pt(SO_4)_2$, as well as in other oral route studies (Holbrook *et al.*, 1975; Reichlmayr-Lais *et al.*, 1992; US EPA, 1977). As might be expected, where compared, oral administration of soluble salts led to higher blood and tissue Pt levels versus insoluble ones (Reichlmayr-Lais *et al.*, 1992; US EPA, 1977).

The intra-tissue and cellular distribution of Pt remains essentially undetermined. Limited information is available from a series of experiments conducted by Artelt *et al.* (1999). In rats, following intratracheal administration of a Pt-alumina, 2–5% of Pt in plasma was associated with complexes of molecular weight <60 kDa, with the remaining fraction associated with higher molecular weight complexes. When rat plasma was incubated with the tetrachloroplatinate salt K_2PtCl_4, high molecular weight complexes ranging from 60 to 900 kDa were detected, which may have included ones with serum albumin. High molecular weight complexes (>63 kDa) were also found in lung tissue and bronchiolar lavage cells, following intratracheal administration of Pt-alumina.

5.4

TRANSFORMATION IN BIOLOGICAL SYSTEMS

As an element, Pt is not metabolised within the body. However, Pt compounds in biological milieu may undergo various transformations including hydrolysis, ligand exchange, and oxidation state changes. Both reversibly bound entities, and irreversible coordinate covalent complexes, can be formed with proteins, amino acids, and nucleic acids. Pt is known to be able to complex to amino acids via imidazole (*e.g.*, histidine), sulfhydryl (*e.g.*, cysteine), amino and carboxyl groups. The specific effect of the immunogenic haptenisation of proteins by reactive Pt species is addressed in Chapter 6; there are some data suggesting that reactivity toward human serum albumin as a target ligand may be important (Grootveld, 1985), but alternate immune system protein targets have been postulated for allergenic transition metals (Chipinda *et al.*, 2011).

Due to the strong affinity of Pt for 'soft ligands' including halogens, it is theoretically possible that non-chloride Pt species might be converted to chloroplatinates in chloride containing body-fluids. However, there is a current lack of robust experimental investigations able to test this hypothesis. The absence of hypersensitivity reactions in workers exposed to non-chloroplatinate Pt salts suggests that this phenomenon may not be biologically significant even if it does occur to some extent.

5.5

EXCRETION

Inhaled low solubility Pt forms mainly undergo mucociliary clearance from the respiratory tract, followed by translocation into the GI tract and then faecal excretion. Based on human data, elimination of soluble Pt salts involves a biphasic process, with additional renal excretion being evident. In certain cases, renal excretion may be relevant to observed patterns of nephrotoxicity, *e.g.*, for soluble hexachloroplatinate salts (see also Chapter 6), and for the platins including cisplatin (refer to Section 5.7).

HUMAN STUDIES

Schierl *et al.* (1998; 1999) investigated urinary excretion in groups of workers from a platinum refinery and catalyst production company exposed to soluble Pt compounds (mainly K_2PtCl_4 and $Pt(NO_3)_2$). End-shift Pt urinary excretion in highly exposed individuals was up to 1000-fold of baseline (ranging up to 6270 ng/g creatinine for measured airborne exposures of 0.8 to 7.5 µg/m^3). The same investigators (1998) found that in volunteers exposed by inhalation (4-hour duration) to a soluble chloroplatinate [$(NH_4)_2PtCl_6$] elimination occurred with a rapid steep increase in urinary Pt (15 to 100-fold), reaching its maximum about ten hours after the exposure. Clearance appeared to be biphasic, with a half-life of the first phase being around 2 days. However, it must be noted that these studies involved only a limited number of subjects. Based on the above studies and biomonitoring data, longer-term elimination modes for some Pt tissue depots are also likely (see also Biological Monitoring).

OTHER DATA

In rats subjected to short-term inhalation of radiolabelled Pt and soluble and insoluble Pt compounds (particulate diameter around 1 µm) most of the radiolabel was cleared from the respiratory tract by mucociliary action and eliminated without gastro-intestinal absorption (Moore *et al.*, 1975a). Insoluble platinum compounds were retained longer in the lungs than soluble ones, with the latter exhibiting some degree of urinary excretion. Clearance was biphasic: an initial rapid phase (20-40% by 24 hours) was followed by a slower phase whereby after ten days more than 90% of the radiolabel had been excreted. In a similar manner to the acute studies, mucociliary clearance and subsequent elimination in the faeces accounted for about 98% of the Pt dose in a study where rats inhaled elemental Pt-coated alumina particles for 90 days (Artelt *et al.*, 1999). Oral administration of either $PtCl_4$ or $Pt(SO_4)_2$ to rodents also results in rapid clearance through the gastrointestinal tract (Moore *et al.*, 1975b; Lown *et al.*, 1980).

5.6

BIOLOGICAL MONITORING

Biological monitoring of PGM workers has shown Pt levels in blood, serum, and urine to be considerably higher than those in the general population. Pt concentrations in biological fluids appear to rise with increasing workplace exposure and so represent a useful marker for exposure. However, no robust relationship has been established between biomonitored levels and development of platinum salt sensitisation.

WORKERS

Several studies have reported Pt concentrations in the blood, serum, and urine of workers exposed to Pt compounds, the results of which have been reviewed by Killunen and Aitio (2015), and are shown in Table 5-1. According to the US CDC, Pt-industry and precious-metal workers had urinary concentrations about 1000 times higher than the general population.

Elevations in urinary Pt concentrations have been associated with handling of cisplatin and carboplatin by pharmacy and other hospital personnel (US CDC, 2013).

As can be seen in Table 5-1, blood- and urinary-Pt levels in Pt workers are often considerably higher than the background levels in the general population (compare to Section 5.6). Most of the Pt in biological fluids of Pt-exposed workers is probably due to inhalation augmented by translocated oral intake, but dermal exposures may make a smaller contribution.

Pt concentrations in biological fluids appear to rise with increasing exposure (Merget *et al.*, 2000; Petrucci *et al.*, 2005). However, a quantitative relationship between concentrations in workplace air versus those in biological fluids—which would allow the derivation of biological monitoring guidance values—has not been established (Kiilunen *et al.*, 2015). Neither blood-Pt levels nor hair-Pt concentrations have proven to be particularly useful biomarkers of worker exposure (Merget *et al.*, 2002; Petrucci *et al.*, 2005).

As evident from Table 5-1, great variability appears to exist in blood- and urinary-Pt levels in healthcare workers handling platins. It is unclear whether this is due to less accurate analytical measurements in earlier studies, or to differences in protective equipment and workplace hygiene practices across these groups (see Chapter 6).

Schierl *et al.* (1998) have suggested that, as with patients given cisplatin (Schierl *et al.*, 1995), there might be a long-term Pt pool in workers exposed to Pt salts, as Pt concentrations in former workers remain elevated for several years post-exposure (see Table 5-1). It is notable that these same workers exhibited no signs of post-exposure sensitisation, and no other reports exist which reliably correlate biomonitored systemic Pt levels and hypersensitivity.

In summary, biomonitoring for systemically absorbed Pt (*i.e.*, as a marker of total internal dose) is certainly feasible, relatively uncomplicated, and high sensitivity methods exist (see also references in Table 5-1). However, associated reference values related to acceptable exposures have not been widely agreed to date. Biomonitoring techniques may be particularly useful where exposures to higher toxicity Pt compounds occur, *e.g.*, to platin

5.6

TABLE 5-1: PLATINUM CONCENTRATIONS IN THE BIOLOGICAL FLUIDS OF WORKERS EXPOSED TO PLATINUM IN VARIOUS OCCUPATIONAL SETTINGS (ADAPTED FROM KILLUNEN *ET AL.*, 2015)

Occupational setting	Biological sample type	Average/Median Concentration, ng/l [a] (Range/Maximum, ng/l)	Reference
Vehicle emission catalyst (VEC) or Process catalyst (PC) production			
VEC production	Serum	14-80 (< 500)	Merget *et al.*, 1999, 2000, 2002
Preparation of coating solutions (VEC and PC)	Blood Serum	110 80	Petrucci *et al.*, 2004, 2005
VEC coating	Blood Serum	380-2900 1550	
Adsorption on substrate (PC)	Blood Serum	110-170 40	
Recycling of spent catalysts	Blood Serum	210-240 150	
Refinery workers			
Refinery/Catalyst	Urine	170-6270 [b,c] 10-170 [b, d] 16-230 [b, e]	Schierl *et al.*, 1998
Precious metal workers	Blood Urine	246 (152-423) 470 (210-1180) [b]	Farago *et al.*, 1998
Traffic workers			
Highway maintenance	Blood Urine	145 (126-158) 58 (22-135) [b]	Farago *et al.*, 1998
Traffic police officers	Urine	5 (0.3-14)	Iavicoli *et al.*, 2004a
Healthcare workers			
Dental	Serum Urine	<5-2120 [f] <10-30 (170)	Begerow *et al.*, 1999; Iavicoli *et al.*, 2004b
Hospital staff (nurses, pharmacists, etc.) [g]	Blood Urine	470-3800 (13300) 13-1300	Ensslin *et al.*, 1994; Nygren and Lundgren, 1997; Pilger *et al.*, 2000; Turci *et al.*, 2002
	Urine	10220 (600-23100)	Venitt *et al.*, 1984

[a] Unless stipulated otherwise.
[b] Normalised to ng Pt/g creatinine.
[c] Workers with high exposures.
[d] Workers with previous high exposures (2-6 years post-high exposure).
[e] Workers with low exposures.
[f] Single high outlier result (2120 ng/L) reported by Iavicoli et al., 2004b
[g] Exposed to platins during preparation and/or administration of therapeutic doses.

5.6

BIOLOGICAL MONITORING

anticancer agents, where there is a need to evaluate even low-level exposure by all routes including via the skin as well as inhalation. In contrast, its utility specifically as a monitor for platinum salt sensitivity risk is low.

GENERAL POPULATION

This section briefly discusses background exposures, some of which may potentially influence workplace monitoring interpretation.

For the general population, without occupational exposure, the diet is a key source of Pt exposure. Pt concentrations in food and drinking water vary widely with geographic location, resulting in considerable variation in intakes (Kiilunen *et al.*, 2015; Vaughan and Florence, 1992; Ysart *et al.*, 1999). Related Pt intakes were estimated to be around 0.02 µg/day in the UK (Ysart *et al.*, 1999) and around 1.44 µg/day in Australia (Vaughan and Florence, 1992). Uptake may also be significant where platinum-containing dental alloy restorations are present (Becker *et al.*, 2003; Begerow *et al.*, 1999; Schierl, 2001; Herr *et al.*, 2003), and these should always be considered in the interpretation of biomonitoring data. Gold-platinum dental restorations have been associated with 5-12-fold increases in urinary Pt (US CDC, 2013).

Ambient air is a less important source of Pt exposure for the general populace, with average airborne concentrations typically ranging between 0.3-30 pg/m^3 (Wiseman and Zereini, 2009), associated largely with limited release of Pt from automobile catalytic converters.

Typical urinary Pt levels range from 1 to 20 ng/l in non-occupationally exposed populations, whereas blood or serum levels have been reported to range from around 1 to 7 ng/l (Messerschmidt *et al.*, 1992; Schaller *et al.*, 1992). More recently (2013, 2014), the US CDC reported that urinary Pt levels for the US population were under the limits of detection (*i.e.* below 9-70 ng/l). Biomonitoring figures available for 2009-2010, showed that the 75th and 95th percentile urinary Pt values were <LOD and 16 ng/l, respectively, and uncorrelated with subject age suggesting that body burden does not increase with age (US CDC, 2014). In 2014, CDC announced that Pt biomonitoring results will no longer be reported due to these low levels of detection in the general population. Readers are referred to the datasets in such references for detailed information on background levels in various populations.

5.7

TOXICOKINETICS (PHARMACOKINETICS)
OF Pt CANCER THERAPY DRUGS (PLATINS)

TOXICOKINETICS (PHARMACOKINETICS) OF Pt CANCER THERAPY DRUGS (PLATINS)

A significant amount of information is available for the platins, and in particular the key drugs cisplatin, carboplatin and oxaliplatin, some of which is briefly summarised here. The reader is referred to standard pharmacology texts for more detailed information.

In relation to their absorption characteristics, the profile established from studies of intravenously administered platins is of limited relevance to occupational contexts (in which exposure to these compounds occurs mainly by the inhalation and dermal routes). Based on clinical information, the inhalation bioavailability of unmodified platins is not high, but is sufficient to be relevant to worker protection considerations. It is thought that platins are not significantly absorbed through intact skin (Simonetti *et al.*, 2009), but their high toxicity (potential carcinogenicity) requires that precautionary protection strategies are applied to control occupational skin exposures.

When parenterally injected, platins are generally rapidly distributed in the blood to other tissues (Calvert *et al.*, 1993; Chabner *et al.*, 2001) though this is most rapid for cisplatin and carboplatin. Cisplatin and oxaliplatin are both extensively bound to plasma proteins, with less binding evident for carboplatin (Chabner *et al.*, 2001). While all platins distribute to the kidneys, they distribute differentially to other organs including lungs, liver, spleen, and testes (Chabner *et al.*, 2001; Tinker *et al.*, 1990). Cisplatin's hallmark renal toxicity seems to be attributable to the compound's specific pattern of renal accumulation, urinary excretion, and particularly its renal tubular secretion (McKeage, 1995), which differs from that of carboplatin and oxaliplatin (Calvert *et al.*, 1993; Graham *et al.* 2000). At steady state, oxaliplatin has the largest volume of distribution [295–812 L], followed by carboplatin [176 L], and cisplatin [52 L] (Calvert *et al.*, 1993; Graham *et al.* 2000). As all platins have been shown to be foetotoxic, it is assumed that they can cross the placenta in toxicologically significant amounts (Pascual *et al.* 2001).

The biotransformation behaviour of platins is well studied but is complex, typically first involving the creation of reactive Pt complexes (including aquated forms).

Other texts provide further information (*e.g.*, Calvert *et al.*, 1993; Chabner *et al.*, 2001).

In the case of therapeutic administration via the intravenous route, renal excretion constitutes the primary elimination route for oxaliplatin and carboplatin; accounting for greater than 50 or 70%, respectively, of total clearance (Calvert *et al.*, 1993; Graham *et al.*, 2000; McKeage, 1995). Initial clearance is rapid for both (within hours), but terminal half-life is longer, circa 6-26 days (Graham *et al.*, 2000; McKeage, 1995). Cisplatin undergoes comparatively less renal clearance (11-32% of cisplatin is eliminated in the urine within 24 hours), reflecting its extensive metabolism and extensive tissue binding (Graham *et al.*, 2000; McKeage, 1995).

5.8

TOXICOKINETICS OF NON-PLATINUM PGMs

For PGMs other than Pt, it should be noted that few TK data are available for metallic or ionic forms, particularly in relation to the inhalation route—the fullest, but incomplete, dataset exists for Pd. In common with Pt, other PGMs are not metabolised but where relevant some commentary is provided on their biological system transformation and reactivity behaviour. The outcomes of general population biomonitoring studies specifically related to low-level environmental releases of PGMs are of limited relevance to occupational contexts, *e.g.*, regarding baseline value variance in a local worker group, and are therefore not discussed here. Neither does this section address organo-PGM complexes developed for pharmaceutical applications.

PALLADIUM AND ITS COMPOUNDS

No quantitative data relevant to occupational exposure are available on the absorption of Pd or Pd compounds in humans, although low µg/l serum concentrations have been associated with Pd use in dental implants (Daunderer, 1993). Studies by Moore *et al.* (1974, 1975) showed that the water-soluble compound $PdCl_2$ was poorly absorbed after a single oral dose to rats (<0.5% of the initial oral dose), but administration via the intratracheal and inhalation routes was reported to result in relatively higher absorption (up to 20%). Reliable studies of systemic absorption via the dermal route on Pd or Pd compounds have not been published, but there are reasons to expect at least limited percutaneous absorption potential for simple soluble Pd compounds. Overall, experimental data indicate that in comparative terms across water-soluble analogues, Pd compounds may be more bioavailable than their Pt counterparts.

After intravenous administration of soluble Pd compounds to rats, rabbits or dogs, Pd was detected in the kidney, liver, spleen, lymph nodes, adrenal gland, lung and bone (Moore *et al.* 1974, 1975b; WHO, 2002). Whereas, in a 4-week rat feeding study with insoluble PdO, measurable levels were found only in the kidney. Dietary administration to rats of high levels of the water-soluble palladium salts $PdCl_2$ and $PdSO_4$ (equivalent to ~700 mg/kg-bw/day Pd) resulted in the greatest Pd levels being detected in the kidney followed, in descending order, by the liver and spleen. Much lower concentrations were evident for insoluble PdO (Holbrook, 1977). A similar pattern of distribution mainly to the kidney has been demonstrated for soluble hexachloropalladate salts (Iavicoli *et al.*, 2009). Transplacental distribution in rats has been demonstrated following single intravenous doses of $^{103}PdCl_2$ (Moore *et al.*, 1974, 1975b).

Ionic Pd is relatively reactive, and can complex with various macromolecules including amino acids, *e.g.*, cysteine or methionine and proteins (particularly at their sulfhydryl centres), and with nucleic acids. Although in vitro experiments have shown Pd^{2+} binding to DNA (WHO, 2002), this is not reflected in corresponding genotoxicity for the simple soluble salts such as tetrachloropalladates (EPMF Precious Metals Consortium, unpublished data; see also Chapter 6); it is postulated that the relatively higher reactivity of this ion instead results in more immediate reactivity with biomolecules other than DNA (which is more protected in cellular location).

5.8

TOXICOKINETICS OF NON-PLATINUM PGMs

Animal studies, predominantly with soluble Pd salts show excretion primarily via the faeces due to low absorption in the case of oral administration (WHO, 2002; Iavicoli *et al.*, 2009), whereas when administered intravenously Pd excretion is via the urinary route (WHO, 2002). Half-lives calculated for the elimination of palladium from rats ranged from 5 to 12 days.

Biomonitoring data (Begerow *et al.*, 1999) show that urinary excretion of palladium was significantly elevated in occupationally-exposed dental technicians compared to unexposed controls (mean Pd concentration 135.4 ± 183.5 ng/l versus 31.0 ± 10.8 ng/l, respectively). However, a more recent study found no similar increases in those handling dental alloys (Iavicoli *et al.* 2004). Data from mining and refinery operations are sparse. Published blood and urinary monitoring data (WHO, 2002) indicate detectable urinary levels only in refinery workers, though reported Pd concentrations were low (mean 1.07 µg/l; maximal 7.41 µg/l). Background levels in human tissues and biological fluids have been reviewed (Umemura *et al.*, 2015).

IRIDIUM RHODIUM RUTHENIUM

TK data for the remaining PGMs are fragmentary. Absorption characteristics appear to be similar to those described for Pt and Pd, with comparable tissue distribution patterns to those PGMs as well. It is reasonable to expect that more water-soluble forms will exhibit greater systemic bioavailability by all routes.

A pattern of low inhalation bioavailability similar to that of Pt was evident for elemental iridium (Casarett, 1960; Kreyling *et al.*, 2002). Iavicoli *et al.* (2012) studied iridium tissue distribution and excretion in female rats following oral exposure to soluble form of Ir ($IrCl_3$ hydrate). Distribution occurred mainly to the kidney and spleen, with lesser amounts found in the lungs and liver.

In comparison to K_2PtCl_4, a rhodium salt ($RhCl_3.xH_2O$) showed lower skin permeation metrics in an in vitro model using human skin samples (Franken *et al.*, 2014).

Ionic forms of rhodium, and in particular Rh^{2+} and Rh^{3+}, have an affinity for protein sulphhydryl groups (Howard *et al.*, 1976) and nucleic acids (DECOS, 2002), which for example is evidenced by the DNA binding properties of certain Rh(III) compounds. A few limited human biomonitoring studies have been published on Rh (*e.g.*, Iavicoli *et al.*, 2007) related to low-level exposures from traffic emissions.

A TK study of the simple salt $^{106}RuCl_3.xH_2O$ (Furchner *et al.*, 1971) in rodents, dogs and primates administered by the oral, intraperitoneal, and intravenous routes demonstrated similar TK profiles to those of Pt and Pd, with relatively uniform inter-species data. Oral absorption was low (up to around 3%), with elimination in the faeces consequently identified as the major excretory route. Human volunteer studies involving oral administration indicate that some ruthenium complexes, *e.g.*, nitrosylruthenium and citrate complexes, are more extensively absorbed than simple Ru salts, including chlororuthenates (Yamagata *et al.*, 1969).

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