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TOXICOLOGICAL REVIEW

OF

HALOGENATED PLATINUM SALTS AND PLATINUM COMPOUNDS

(CAS No. various)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

January, 2009

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LIST OF ABBREVIATIONS AND ACRONYMS

AIC	Akaike's information criterion
AOO	acetone and olive oil
API	α1-Proteinase inhibitor
AAS	atomic absorption spectrometry
BMC	benchmark concentration
BMCL	benchmark concentration, lower 95% confidence limit
BMD	benchmark dose
BMDL	benchmark dose, lower 95% confidence limit
BMDS	benchmark Dose Software
BMR	benchmark response
BSA	bovine serum albumin
CASRN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary
CI	confidence interval
CPO	chemical process operator
CV	coefficient of variation
DF	deposition fractions
DMSO	dimethylsulfoxide
DNCB	2,4-dinitrochlorobenzene
FEF	forced expiratory flow
FEV	forced expiratory volume
FVC	forced vital capacity
GFR	glomerular filtration rate
GI	gastrointestinal
GM	geometric mean
GSD	geometric standard deviation
HSA	human serum albumin
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IFN	interferon
IL	interleukin
ICP-MS	inductively coupled-mass spectrometry
IRIS	Integrated Risk Information System
KLH	keyhole limpet hemocyanin
LCL	lower confidence limit
LD_{50}	median lethal dose
LOD	Llmit of detection
LOQ	limit of quantitation
LOAEL	lowest-observed-adverse-effect level
MCV	mean corpuscular volume
MDI	methane-4,4'-diisocyanate
MHC	major histocompatibility complex
MMAD	mass median aerodynamic diameter
MN	micronucleus
NOAEL	no-observed-adverse-effect level
NIST	National Institute of Standards and Technology

OSHA	Occupational Safety and Health Administration
OVA	ovalbumin
PBMC	peripheral blood mononuclear cells
PBPK	physiologically based pharmacokinetic
PCA	passive cutaneous anaphylaxis
PCNA	proliferating cell nuclear antigen
PD	provocative dose
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PGE	Pt group element
PHA	phytohemagglutin
PLN	popliteal lymph node assay
PM	particulate matter
POD	point of departure
POR	prevalence odds ratios
Pt	platinum
RAST	radioallergenosorbent test
RfC	reference concentration
RfD	reference dose
ROS	reactive oxygen species
SD	Standard deviation
SE	Standard error
SPT	skin prick test
SPTC	skin prick test conversion
TLV	threshold limit value
TMA	trimellitic anhydride
TNF	tumor necrosis factor
TPC	tetraamine Pt dichloride
TWA	time-weighted average
UF	uncertainty factor
U.S. EPA	U.S. Environmental Protection Agency

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to halogenated platinum (Pt) salts and Pt compounds. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of halogenated Pt salts and Pt compounds.

The intent of Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response,* is to present the major conclusions reached in the derivation of the reference dose, reference concentration, and cancer assessment, where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing the quality of data and related uncertainties. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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REVIEWERS

This document and the accompanying IRIS Summary has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of halogenated Pt salts and Pt compounds.

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of halogenated platinum (Pt) salts and Pt compounds. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and other exposure durations, and a carcinogenicity assessment.

The RfD and RfC, if derived, provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m^3) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values are generally derived for chronic exposures (up to a lifetime), but may also be derived for acute (#24 hours), short-term (>24 hours up to 30 days), and subchronic (>30 days up to 10% of lifetime) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified. Unless specified otherwise, the RfD and RfC are derived for chronic exposure duration.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure may be derived. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates may be derived from the application of a low-dose extrapolation procedure. If derived, the oral slope factor is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, an inhalation unit risk is a plausible upper bound on the estimate of risk per $\mu g/m^3$ air breathed.

Development of these hazard identification and dose-response assessments for halogenated Pt salts and Pt compounds has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA Guidelines and Risk Assessment Forum Technical Panel Reports that may have been used in the development of this assessment include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Interim Policy for*

Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000a), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000b), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000c), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006a), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

The literature search strategy employed for this compound was based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through August 2008.

2. CHEMICAL AND PHYSICAL INFORMATION

Pt is a third row transition metal and is a member of the Pt group metals (ruthenium, rhodium, palladium, osmium, iridium, and Pt) (Giandomenico and Matthey, 1996). Its average concentration in the rocky crust of the earth is approximately 0.001–0.005 mg/kg (WHO, 1991). Elemental Pt is a silver-gray, lustrous, ductile, malleable metal (O'Neil, 2001). Pt metal is chemically stable in air even at high temperatures and is unaffected by most acids (Czerczak and Gromiec, 2001; WHO, 1991). When present in compounds, Pt exists most commonly in the +2 and +4 oxidation states (Czerczak and Gromiec, 2001; Giandomenico and Matthey, 1996). Chemical structures and selected chemical and physical properties of halogenated Pt salts and Pt compounds are listed in Table 2-1.

Pt is found in nature both in the metallic form and in minerals such as sperrylite, cooperate, braggite, ferroplatinum, moncheite, rustenburgite, and vysotskite (Renner et al., 2005; Seymour and O'Farrelly, 2001; WHO, 1991). During manufacture, Pt group metals in the ore are first concentrated, and are then treated with a highly oxidizing acid solution, such as aqua regia, hydrochloric acid-chlorine, or hydrochloric acid-bromine, to dissolve some or all of the Pt group metals (Renner et al., 2005; Czerczak and Gromiec, 2001; Seymour and O'Farrelly, 2001). Hexachloroplatinic and tetrachloroplatinic acids are water-soluble forms of Pt salts that can be produced in this process (see Table 2-1 for structures). The metals are then separated out using selective dissolution and precipitation techniques. Pt is typically precipitated from solution through the addition of ammonium chloride, which precipitates ammonium hexachloroplatinate from solution under refinery conditions.

Both soluble and insoluble Pt compounds can be present in environmental and occupational samples. Soluble Pt is measured with quantitative techniques after extracting samples into a solution (e.g., water, dilute hydrochloric acid, or nitric acid). Therefore, soluble Pt is an operationally-defined fraction of Pt in which many different species of Pt can be present depending on the extraction solution (see *Analysis of Pt in Ambient Air and Source Samples* below for further discussion). In this document, the term *soluble Pt compounds* primarily includes $Pt(SO_4)_2$, tetraamine Pt dichloride (TPC) ($[Pt(NH_3)_4]Cl_2$), and the halogenated Pt salts, compounds for which there are published kinetic or toxicity data. When samples contain halogenated Pt salts, these compounds are likely to be a portion of the soluble Pt reported because of their solubility in water and other common extraction solutions (see Table 2-1 for solubility of individual compounds). Pt salts of any of the halogen elements are collectively referred to as halogenated Pt salts. Salts of the ions $[PtCl_4]^{2-}$ and $[PtCl_6]^{2-}$ are the most important commercial Pt compounds, although there are also Pt salts of other halides (e.g., bromine) (Cotton and Wilkinson, 1988; Cleare et al., 1976). Halogenated Pt salts are generally considered

Table 2-1. Physical properties of Pt and selected Pt compounds

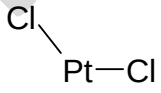
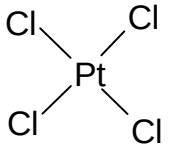
Name	Pt	Pt(II) oxide	Pt(IV) oxide	Pt(II) chloride	Pt(IV) chloride
CASRN	7440-06-4	12035-82-4	1314-15-4	10025-65-7	13454-96-1; 37773-49-2
Synonyms	Platin; platinum black; platinum sponge; liquid bright platinum	Platinum oxide; platinum monoxide	Platinum dioxide; platinic oxide; Adam's catalyst	Platinum dichloride; platinous chloride; muriate of platinum	Platinum tetrachloride; platonic chloride
Structure	Pt	Pt=O	O=Pt=O		
Molecular weight	195.078	211.08	227.08	265.98	336.89
Molecular formula	Pt	PtO	PtO_2	$PtCl_2$	$PtCl_4$
Halogenated Pt salt	No	No	No	No; halogenated Pt, not a salt	Yes
Form	Silver-gray, lustrous, malleable, and ductile metal; also prepared as a black powder and spongy masses	Black tetrahedral crystal	Black powder; hexagonal crystals	Grayish-green to brown powder; hexagonal crystals	Red-brown cubic crystals
Melting point	1,768.2°C (boiling point = 3,825°C)	325°C (decomposes)	450°C	581°C	327°C (decomposes)
Density	21.5 g/cm^3	14.1 g/cm^3	11.8 g/cm^3	6.0 g/cm^3	4.30 g/cm^3
Water solubility[a]	Insoluble	Insoluble	Insoluble	Insoluble	142 g/100 g H_2O at 25°C
Other solubility[a]	Insoluble in mineral and organic acids; reacts with boiling aqua regia	Insoluble in ethanol; soluble in aqua regia	Soluble in concentrated acid and dilute alkaline solutions	Insoluble in ethanol; soluble in hydrochloric acid and ammonium hydroxide	Soluble in ethanol

Table 2-1. Physical properties of Pt and selected Pt compounds

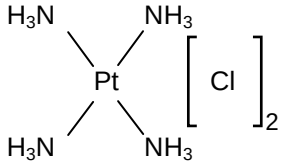
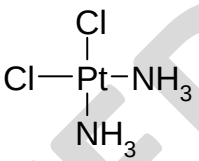
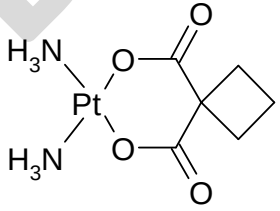
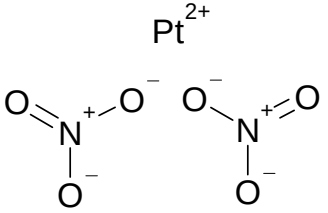
Name	Tetraamine Pt dichloride	Cisplatin	Carboplatin	Pt dinitrate
CASRN	13933-32-9	15663-27-1	41575-94-4	18496-40-7
Synonyms	Tetraammine platinous chloride; tetraammine-dichloroplatinum(II); tetraammineplatinum(II) chloride; TPC	*cis*-Diamminedichloroplatinum; *cis*-platinum II; *cis*-DDP; CACP; CPDC; DDP; briplatin; cismaplat; cisplatyl; citoplatino; lederplatin; neoplatin; platamine; platinex; platiblastin; platinol; platinoxan; platistin; randa	1,1-Cyclobutanedicarboxylic acid platinum complex; *cis*-diammine (1,1-cyclobutane-dicarboxylato) platinum(II); CBDCA; JM-8; Paraplatin	Not available
Structure				
Molecular weight	334.109	300.05	371.25	319.088
Molecular formula	$[Pt(NH_3)_4]Cl_2$	$PtCl_2(NH_3)_2$	$PtC_6H_6O_4(NH_3)_2$	$Pt(NO_3)_2$
Halogenated Pt salt	No halide is present as an ion and not a ligand coordinated to Pt (Linnett and Hughes, 1999; Cleare et al., 1976); therefore, halogenated complex salt	No	No	No
Form	White, crystalline powder	Deep yellow solid	White crystals, soluble in water	Not available
Melting point	250°C (decomposes)	270°C (decomposes)	Not available	Not available
Density	Not available	Not available	Not available	Not available
Water solubility[a]	20 g/100 mL H_2O	0.253 g/100 g H_2O at 25°C	Approx. 15 mg/mL	Not available
Other solubility[a]	Insoluble in ethanol	Insoluble in most common solvents; soluble in dimethyformamide	Not available	Not available

Table 2-1. Physical properties of Pt and selected Pt compounds

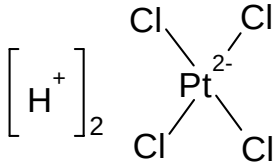
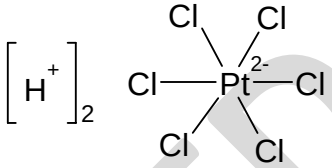
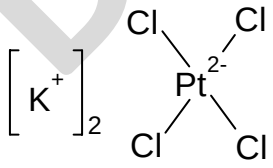
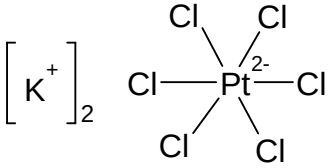
Name	Tetrachloroplatinic(II) acid	Hexachloroplatinic(IV) acid	Potassium tetrachloroplatinate	Potassium hexachloroplatinate
CASRN	Not available	16941-12-1	10025-99-7	16921-30-5
Synonyms	Dihydrogen tetrachloroplatinate(II)	Hexachloroplatinic acid hexahydrate; dihydrogen hexachloroplatinate(IV)	Potassium tetrachloroplatinate(II); platinous potassium chloride; potassium platinochloride; potassium chloroplatinite	Potassium hexachloroplatinate(IV); Platinic potassium chloride; potassium platonic chloride
Structure				
Molecular weight	336.90	409.81	415.09	485.99
Molecular formula	H_2PtCl_4	$_2PtCl_6.6H_2O$	K_2PtCl_4	$_2PtCl_6$
Form	Not available	Brownish-yellow hygroscopic crystals	Ruby-red crystals	Orange-yellow crystals or yellow powder
Halogenated Pt salt	Yes	Yes	Yes	Yes
Melting point	Not available	60°C	500°C (decomposes)	250°C (decomposes)
Density	Not available	2.43 g/cm^3	3.38 g/cm^3	3.5 g/cm^3
Water solubility[a]	Not available	140 g/100 g H_2O at 18°C	Soluble in water	0.77 g/100 g H_2O at 20°C
Other solubility[a]	Not available	Soluble in ethanol and ether	Soluble in ethanol and ether	Insoluble in ethanol

Table 2-1. Physical properties of Pt and selected Pt compounds

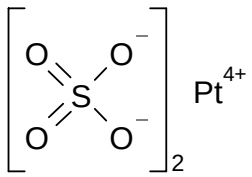
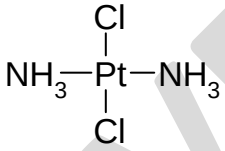
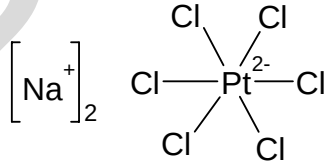
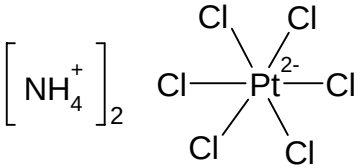
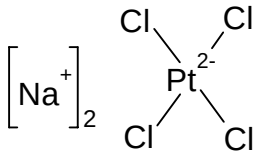
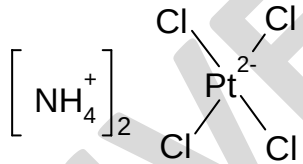
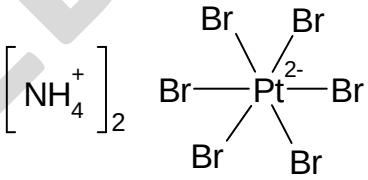
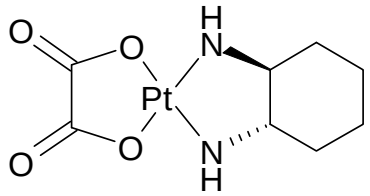
Name	Platinum(IV) sulfate	Transplatin	Sodium hexachloroplatinate	Ammonium hexachloroplatinate
CASRN	7446-29-9	14913-33-8	16923-58-3	16919-58-7
Synonyms	Platinic sulfate; Sulfuric acid, platinum(4+) salt (2:1)	trans-Diamminedichloroplatinum; trans-diamminedichloro-platinum(II); trans-DDP; trans-dichlorodiammineplatinum; trans-dichlorodiammine-platinum(II); trans-platinum-diammine dichloride; trans-platinum(II)diammine dichloride	Disodium hexachloroplatinate; sodium hexachloroplatinate (IV); platinate(2-), hexachloro-, disodium, (OC-6-11)-	Ammonium chloroplatinate; ammonium platinic chloride; ammonium platinum chloride; ammonium hexachloroplatinate(IV); diammonium hexachloroplatinate(2-); diammonium platinum hexachloride; platinate(2-), hexachloro-diammonium, (OC-6-11)-; platinum ammonium chloride; quaternium-17; platinic sal ammoniac
Structure				
Molecular weight	387.204	300.04	453.78	443.88
Molecular formula	$Pt(SO_4)_2$	$PtCl_2(NH_3)_2$	Na_2PtCl_6	$(NH_4)_2PtCl_6$
Halogenated Pt salt	No	No	Yes	Yes
Form	Hygroscopic, greenish-black mass	Pale yellow solid	Yellow, hygroscopic crystals	Orange-red crystals or yellow powder
Melting point	Not available	Decomposes at 270°C	Not available	Decomposes at 380°C
Density	Not available	Not available	Not available	3.065 g/cm^3
Water solubility[a]	Soluble in water	0.036 g/100 g H_2O at 25°C	53 g/100 g H_2O at 16°C	0.5 g/100 g H_2O at 20°C
Other solubility[a]	Soluble in dilute acids, alcohol, ether	Soluble in dimethyl sulfoxide and dimethyl formamide	Soluble in alcohol	Practically insoluble in alcohol

Table 2-1. Physical properties of Pt and selected Pt compounds

Name	Sodium tetrachloroplatinate	Ammonium tetrachloroplatinate	Ammonium hexabromoplatinate	Oxaliplatin
CASRN	10026-00-3	13820-41-2	17363-02-9	61825-94-3
Synonyms	Platinate(2-), tetrachloro-, disodium, (SP-4-1)-; disodium tetrachloroplatinate; platinous sodium chloride; sodium chloroplatinite; sodium tetrachloroplatinate(II) tetrahydrate	Ammonium platinous chloride; ammonium chloroplatinate(II); bis(ammonium) tetrachloroplatinate(2-); diammonium tetrachloroplatinate; platinate(2-), tetrachloro-, diammonium, (SP-4-1)-	Ammonium hexabromoplatinate (IV); Platinate(2-), hexabromo-, diammonium (OC-6-11)-	(SP-4-2-(1R-trans))-(1,2-Cyclohexanediamine-N,N')ethanedioato(2-)-O,O')platinum; 1-OHP; Dacplat; Eloxatin; JM-83; Oxalato(1R,2R-cyclo-hexanediammine)platinum(II); Oxalato (trans-1-1,2-cyclohexanediamine)platinum(II); oxalatoplatin; oxalatoplatinum; *cis*-([1R,2R]-1,2-Cyclohexanediamine-N,N') oxalate(2-)-O,O')platinum; platinum, ([1R,2R]-1,2-cyclohexanediamine-.kappa.N, kappa.N') ethanedioato(2-)-kappaO1, kappa O2)-, (SP-4-4)-
Structure				
Molecular weight	454.93	372.97	710.58	397.29
Molecular formula	$Na_2PtCl_4.4H_2O$	$(NH_4)_2PtCl_4$	$(NH_4)_2PtBr_6$	$PtC_8H_{14}N_2O_4$
Halogenated Pt salt	Yes	Yes	Yes	No
Form	Red prisms	Dark ruby-red crystals	Powder	Colorless, thin triangular plates with truncated vertices
Melting point	100°C	140–150°C (decomposes)	Decomposes at 145°C	Not available
Density	Not available	2.936 g/cm^3	Not available	Not available
Water solubility[a]	Soluble in water	Soluble in water	0.59 g/100 g H_2O at 20°C	7.9 mg/mL
Other solubility[a]	Soluble in ethanol	Insoluble in alcohol	Not available	Not available

[a]For solubility, quantitative data are reported in the table when available in the sources examined.

Sources: ChemIDplus (2007, 2006); Hamelers et al. (2006); Lide (2005); Czerczak and Gromiec (2001); Lewis (2001); O'Neil (2001); Johnson Matthey (2000).

soluble and both their solubility and toxicity appear to be related to the halogen-ligands coordinated to Pt and the negative charge of these complexes (Nischwitz et al., 2004; Ravindra et al., 2004; Rosner and Merget, 2000; Cleare et al., 1976). There is a distinction between the halogenated Pt salts and ([Pt(NH3)4]Cl_2), a Pt compound in which halide is present as an ion and not a ligand coordinated to Pt; therefore, $[Pt(NH_3)_4]Cl_2$ is a halogenated complex, not a halogenated Pt salt (Linnett and Hughes, 1999; Cleare et al., 1976). The terms *insoluble Pt* or *insoluble Pt compounds* principally refer to the following compounds for which there are published kinetic or toxicity data: Pt metal, Pt oxide (PtO), Pt dioxide (PtO_2), and Pt dichloride ($PtCl_2$).

Analysis of Pt in Ambient Air and Source Samples

Since the toxicity of some metals, including Pt, is highly dependent on the chemical species in which they are present, analytical techniques need to be applied that have the ability to identify and quantify the species of metals present. These techniques are not readily available and frequently involve research-grade analytical instrumentation and expertise. In the absence of routine laboratory methods for speciation, Pt concentrations in both environmental media and in source samples are most frequently reported as total Pt (i.e., Pt in all chemical forms and oxidation states that were present in the sample). Total Pt is measured in samples following complete sample digestion followed by quantitative determination often using inductively coupled-mass spectrometry (ICP-MS) (Barefoot and Van Loon, 1999). To provide qualitative information regarding the chemical nature of Pt compounds in a sample matrix, investigators have frequently measured soluble and insoluble Pt. These studies involve extracting samples into a solution (e.g., water, dilute hydrochloric acid, or nitric acid) followed by filtration to exclude small Pt-containing particles that are not in solution. The soluble fraction is an operationally-defined fraction of Pt in which many different species of Pt can be present depending on the extraction solution. When extracting into water, Pt salts with halogen- or nitrogen-donor ligands can be present and in the presence of slightly or highly acidic solutions, Pt can be oxidized and brought into solution (WHO, 1991). As such, characterization of Pt from environmental samples as "soluble Pt" does not provide information regarding the chemical species present in a sample. Techniques available from other disciplines are being developed for application to environmental samples in order to identify and quantify the species of metals present (e.g., X-ray absorption fine structure techniques).

Production and Uses of Pt and Pt Compounds

Primary production of Pt (production from mining) in the United States during 2004 was 4,040 kg (worldwide production was 214,000 kg) (George, 2006). The Stillwater Mine and East Boulder Mine located in south-central Montana are the only primary sources of commercial Pt in the United States (George, 2006). Over 70% of the world's primary production of Pt takes place at the Bushveld complex of South Africa (George, 2006; Renner et al., 2005; Seymour and

O'Farrelly, 2001). Secondary production (recovery and recycling) of Pt group metals has become increasingly important due to the rising prices of these metals (George, 2006, 2004; Johnson Matthey, 2006b; Renner et al., 2005). Secondary production of Pt in the United States was 3,080–5,130 kg during 2004 (George, 2004). Total U.S. imports and exports of Pt in 2005 were 86,400 and 20,000 kg, respectively (George, 2006). Workers in the primary and secondary production of Pt may be expected to be exposed to similar conditions since similar selective dissolution and precipitation processes are used in these industries.

The two major uses of Pt metal are in jewelry and automotive emission control catalysts (catalytic converters), which represent approximately 30 and 46%, respectively, of the worldwide demand for Pt as of 2005–2006 (Johnson Matthey, 2007, 2006a; Renner et al., 2005). Use in jewelry has been declining in recent years due to the rising price of Pt (George, 2006, 2004). Pt-based catalysts have been used in gasoline-fueled vehicles in the U.S. since 1975. The Pt content of catalysts used in gasoline-fueled vehicles has decreased from the amounts used in the 1970s due to improvements in catalyst formulations. The Pt content of catalytic converters used in gasoline-fueled vehicles also changes over time depending on the price of Pt and technological issues (e.g., emissions reduction strategies). Pt-based catalysts (e.g., oxidation catalysts and catalyzed wall-flow filters) are being increasingly employed to reduce emissions from diesel vehicles and nonroad engines. Pt is also commercially available as an additive to diesel fuel (i.e., in liquid form), which can be used as an after-market additive for diesel fleets. Other commercial applications of Pt metal include oxidation catalysts in the manufacture of acetic acid, nitric acid, sulfuric acid, and other chemicals; thermocouples; electrical contacts and devices; electrodes; high temperature electrolysis; medical and dental materials; laboratory and industrial apparatus; resistance thermometry; high temperature equipment for use in the glass industry; and ceramic coatings (Renner et al., 2005; Czerczak and Gromiec, 2001; Lewis, 2001; O'Neil, 2001; Seymour and O'Farrelly, 2001). Pt oxidation catalyst technology also is used in other emission control applications such as gas turbines (WHO, 1991).

Hexachloroplatinic acid is the most important of the commercial Pt compounds (Renner et al., 2005). It is prepared by treatment of Pt sponge (metallic Pt in a colloidal form) with aqua regia or moderately concentrated hydrochloric acid saturated with chlorine (Renner et al., 2005; Czerczak and Gromiec, 2001). Hexachloroplatinic acid is used in the manufacture of most Pt compounds and for impregnating catalyst support materials (Renner et al., 2005; Lewis, 2001). In catalytic converters for gasoline-fueled vehicles, metallic forms of Pt and other Pt-group elements (e.g., palladium and rhodium) are contained in a 90% aluminum oxide coating of a honeycomb-type support material made of a high melting point ceramic material (Palacios et al., 2000). In the manufacture of catalytic converters, hexachloroplatinic acid, palladium chloride, and rhodium chloride are impregnated into the aluminum oxide coating and then converted to the metallic forms by reduction in a hydrogen gas stream at high temperatures (Ravindra et al., 2004).

The presence of Pt in dental materials and medical treatments represents a separate category of Pt usage wherein exposure is intentional and the potential toxicity of the form of Pt used may relate to its medical role. The Pt anticancer drugs currently approved for clinical use are cisplatin, carboplatin, and oxaliplatin (see Table 2-1 for chemical structures), although a large number of carboplatin analogues have been developed and tested to various degrees in clinical trials (Sanderson et al., 1996). These drugs have been used to treat testicular, ovarian, head and neck, bladder, lung, prostate, and cervical cancer (Seymour and O'Farrelly, 2001; Giandomenico and Matthey, 1996). They are especially effective against testicular tumors, where long-term remission is achieved in 90% of patients treated. Section 4.4.3 (*Drug Studies*) provides an overview of pharmacokinetic properties of some of the Pt anticancer drugs and adverse effects associated with their use. A comprehensive review of their pharmacokinetic and toxicological properties is beyond the scope of this document, because they are not expected to represent a significant source of environmental exposure to Pt. Another medical use of metallic Pt is in noble metal dental alloys that also contain silver, gold, and palladium (Benemann et al., 2005; Herr et al., 2003; Wataha et al., 1995). Pt content in noble metal dental restorations is known to vary, and has been reported to be as high as 20% (Herr et al., 2003).

Major uses of selected Pt compounds are listed in Table 2-2.

Table 2-2. Major uses of selected Pt compounds

Name	CASRN	Use
Platinum(IV) oxide	1314-15-4	Hydrogenation catalyst (by forming Pt black)
Platinum(II) chloride	10025-65-7	Preparation of Pt salts
Cisplatin	15663-27-1	Chemotherapeutic agent
Carboplatin	41575-94-4	Chemotherapeutic agent
Hexachloroplatinic(IV) acid	16941-12-1	Manufacture of most Pt compounds; impregnating catalyst support materials; electroplating; etching zinc for printing; manufacture of Pt mirrors, indelible ink, and ceramics; in microscopy; as a catalyst for the manufacture of SO_3
Potassium tetrachloroplatinate(II)	10025-99-7	Manufacture of Pt(II) compounds
Potassium hexachloroplatinate(IV)	16921-30-5	In photography; laboratory reagent

Sources: Renner et al. (2005); Lewis (2001); O'Neil (2001); Seymour and O'Farrelly (2001).

Release of Pt from Vehicles Equipped with Catalytic Converters

Vehicles equipped with catalytic converters are thought to represent one of the main sources of Pt in ambient air, especially in areas heavily populated with automotive vehicles (Fritsche and Meisel, 2004; Leśniewska et al., 2004; Rauch et al., 2004; Schins et al., 2004; Gómez et al., 2002; Moldovan et al., 2002; Gómez et al., 2001; Rauch et al., 2001; Zereini et al., 2001; Rauch and Morrison, 2000; Rosner and Merget, 2000; Alt et al., 1993). A comparison of

Pt concentrations in air and airborne-dust samples collected in Germany in 1988 (when catalytic converters were introduced in Germany), 1989, 1992, 1997, and 1998 showed a trend for a continuous increase in Pt concentrations during this period (Zereini et al., 2001). The difference in mean Pt concentrations between air samples collected in 1988 (3 pg/m^3) and 1998 (147 pg/m^3) was about 49-fold (Zereini et al., 2001). Although similar studies of airborne Pt concentration trends in the U.S. were not located, sediment-based data from an urban lake near Boston, Massachusetts (Upper Mystic Lake) support a similar increase in Pt concentrations following widespread use of catalytic converters in the U.S. (Rauch and Hemond, 2003). Deposition rates from 1940 to 1980 were 0.5–0.8 μg/m^2 year (±0.5 standard deviation [SD]) in Upper Mystic Lake. The deposition rate increased after the introduction of catalytic converters and then reached a relatively constant deposition of 7.2 μg/m^2 year (±4 SD) after 1990 (Rauch and Hemond, 2003).

Research on the forms of Pt released from vehicles equipped with catalytic converters has focused predominantly on gasoline engines and, to a lesser degree, on diesel engines (Moldovan et al., 2002; Merget and Rosner, 2001). Release of Pt from three-way catalysts on light-duty gasoline vehicles is thought to occur in a particulate form, mostly as very small particles of Pt metal (i.e., "nanocrystalline metallic Pt") attached to larger particles of aluminum oxide (Artelt and Levsen, 2000; Artelt et al., 1999a). Based on the results of laboratory experiments with gasoline engines equipped with catalytic converters, the largest fractions of aluminum oxide particles containing Pt (43–74%) have been reported to have aerodynamic diameters >10 μm (Artelt et al., 1999a). Since very small amounts of Pt are emitted from catalysts, measurements are usually limited to total Pt. Among the few studies reporting measurements of soluble Pt, investigators have extracted samples into dilute acid solutions (Moldovon et al., 2002; Artelt et al., 1999b). These solutions were filtered to exclude small metallic Pt particles from being considered soluble. In spite of this precaution, metallic Pt that exists on particles smaller than the pore size of the filter were reported as soluble Pt (Artelt et al., 1999b). As discussed earlier in this chapter, the use of an acidic extraction solution can bring some Pt species into solution that were not initially present as strictly water-soluble Pt. A further challenge in interpreting these data is the complex matrix effects provided by motor vehicle exhaust particulate matter (PM). Motor vehicle PM is a largely organic matrix that can provide a hydrophobic coating for trace metals present in the exhaust stream. Extracting this organo-PM in a slightly acidic solution is not expected to liberate all of the relevant Pt in the matrix. When present, halogenated Pt salts would be part of the soluble Pt fraction; however, since no data are available on the Pt species present in the soluble Pt fraction, these data do not provide information on the emissions or ambient concentrations of halogenated Pt salts.

Estimates of the fraction of the total Pt emitted from catalytic converters as soluble Pt compounds have ranged from <1 to <10% (Moldovan et al., 2002; Artelt et al., 1999b). Pt oxides have been estimated to account for <5% of Pt emitted (see review by Rosner and Merget,

2000). As discussed above, the Pt species in the soluble Pt fraction reported in these studies have not been identified. Laboratory experiments have demonstrated the formation of soluble Pt salts after incubating nanocrystalline metallic Pt attached to aluminum oxide particles in physiological saline solutions (Nachtigall et al., 1996).

Levels of Pt in the Environment and Potential for Human Exposure

Levels of total Pt detected in ambient air samples collected in various regions of the world are shown in Table 2-3 (see Ravindra et al., 2004 for a review of environmental Pt group element [PGE] levels). The ultralow levels of Pt in environmental media pose analytical difficulties that have precluded the determination of the chemical form of Pt in ambient air samples (Ljubomirova et al., 2008; Nischwitz et al., 2004, 2003). Therefore, concentrations of total Pt are generally reported and even when there are data on soluble Pt, speciation data are not available to determine the percentage represented by halogenated Pt salts. The Pt levels in ambient air samples shown in Table 2-3 have values in the approximate range of 1–500 pg Pt/m^3 (1×10^{-6} to 500×10^{-6} μg Pt/m^3) with a maximum range of 2740 pg Pt/m^3 in Probst et al. (2001). While most studies of Pt in the environment have been performed in Europe, one recent study of ambient Pt in the U.S. reported concentrations of airborne Pt ranging from 6 to 9 pg Pt/m^3 (Rauch et al., 2005). In contrast, air samples from manufacturing workplaces using Pt have shown much higher values. For example, Merget (2000) reported approximate lower and upper quartile values of 930 and 3,490 ng soluble Pt/m^3 (0.93 and 3.49 μg soluble Pt/m^3) for personal air samples collected from high-exposure workers in a German catalyst production plant. Baker et al. (1990) reported concentrations of airborne Pt in a U.S. precious metals reclamation plant that were also in the μg/m^3 range. Mean air concentrations of Pt salts[1] for sampling locations were between 0.5 and 27.1 μg Pt/m^3 (Baker et al., 1990).

[1]Measured air concentrations of Pt were reported as "salts"; therefore measurements are assumed to be equivalent to soluble Pt in Baker et al. (1999). The ranges of measurements within a sampling location, SDs, and analytical methods were not reported.

Table 2-3. Pt concentrations in air samples

Region	Special features	Pt concentration (pg/m^3, unless indicated otherwise)	Reference
California, USA	—	<0.05	Johnson et al., 1975
Boston, USA	Urban area, PM_{10}	6.9 ± 1.9	Rauch et al., 2005
Tsukuba, Japan	—	14–184 ng/g	Mukai et al., 1990
Dortmund, Germany	Urban areas	0.02–5.1	Alt et al., 1993
Dortmund, Germany	Highway	30	Alt et al., 1993
Munich, Germany	Bus, tramway	0–43.1, mean: 7.3	Schierl and Fruhmann, 1996
Graz, Austria	Tunnel dust	11.0 ± 3.8	Schierl and Fruhmann, 1996
Bruck/Mur, Austria	Tunnel dust	13.0 ± 3.8	Wegscheider and Zischka, 1993
Stuttgart, Germany	Urban area, 1997	68 ng/g	Helmers and Mergel, 1998
Czech Republic	Various sites	9–62	Vlasankova et al., 1999
Italy	—	6.4–38.8	Caroli et al., 2001
Germany	Background level	<2	Rosner and Merget, 2000
Rome	Heavy traffic areas	7.8–38.8	Petrucci et al., 2000
Copenhagen	Heavy traffic, 1993	13	Probst et al., 2001
Copenhagen	Heavy traffic, 1995–1997	250–2,740	Probst et al., 2001
Madrid, Spain	—	<0.1–57.1, mean: 12.8	Gómez et al., 2001
Madrid, Spain	Urban area, PM_{10}	Mean: 7.3	Gómez et al., 2002
Madrid, Spain	Ring road area, PM_{10}	Mean: 17.7	Gómez et al., 2002
Göteborg, Sweden	Urban area, PM_{10}	Mean: 13.1	Gómez et al., 2002
Göteborg, Sweden	Ring road area, PM_{10}	Mean: 4.1	Gómez et al., 2002
Rome	Urban area, PM_{10}	Mean: 8.6	Gómez et al., 2002
Rome	Ring road area, PM_{10}	Mean: 8.1	Gómez et al., 2002
Madrid, Spain	Highway, PM_{10}	15–19	Gómez et al., 2003
Munich, Germany	—	4.4–42.4, mean: 13.6	Dietl et al., 2000
Munich	Tramway, 1993–1994	Mean: 7.3	Schierl, 2000
Munich	Tramway, 1995–1996	Mean: 21.5	Schierl, 2000
Germany	1988	3	Zereini et al., 2001
Germany	1998	147	Zereini et al., 2001
Frankfurt, Germany	PM_{10}, 2001, major street	8.7–28.4, mean: 15.7	Zereini et al., 2004
Frankfurt, Germany	PM_{10}, 2001, side street	4.1–9.5, mean: 6.2	Zereini et al., 2004
Frankfurt, Germany	PM_{10}, 2001, nonurban	3.0–7.9, mean: 5.2	Zereini et al., 2004
Göteborg, Sweden	Urban area, PM_{10}	0.9–19	Rauch et al., 2001
Vienna, Austria	PM_{10}	4.3	Kanitsar et al., 2003
Vienna, Austria	<30 μm	38.1	Kanitsar et al., 2003
Buenos Aires, Argentina	PM_{10}	2.3–47.7, mean: 12.9	Bocca et al., 2006
Buenos Aires, Argentina	Road dust	123.8–486.3 ng/g	Bocca et al., 2006
Bialystok, Poland	Tunnel dust	23.3 ± 3.8 ng/g	Leśniewska et al., 2004
Bialystok, Poland	Road dust	35.9–110.9 ng/g	Leśniewska et al., 2004
Perth, Australia	Road or tunnel dust	53.84–440.46 ng/g	Whitely and Murray, 2003
London	Road dust	101.6–764.2 ng/g	Ward and Dudding, 2004

Source: Modified from Ravindra et al. (2004).

Recent research efforts to determine levels of Pt and other PGEs (e.g., palladium and rhodium) in soils adjacent to heavily traveled roads or sediments receiving runoffs from roads

indicate that concentrations of PGEs may exceed background levels by a factor of 100 or more (Zereini et al., 2007; Whiteley and Murray, 2005; Ek et al., 2004; Fritsche and Meisel, 2004; Leśniewska et al., 2004; Rauch et al., 2004; Ward and Dudding, 2004; Kylander et al., 2003; Whiteley and Murray, 2003; Gómez et al., 2002, 2001; Rauch et al., 2001; Rauch and Morrison, 2000). Based on a review of reported levels of Pt and other PGEs in road dust, soil, vegetation, rainwater, and bodies of water and their sediments, Ravindra et al. (2004) concluded that levels of Pt and other PGEs in the environment have been increasing in parallel with the increased use of Pt and other PGEs in automobile catalysts. Although the Ravindra et al. (2004) conclusions are largely based on exposure data from Europe, lake sediment data from Massachusetts support the same trend for increased levels of Pt and other PGEs in parallel with automobile catalyst use in the U.S. (Rauch and Hemond, 2003). Data from the U.S. indicate that PGE concentrations in roadside soil and dust are comparable to European studies (Ely et al., 2001; Hodge and Stallard, 1986). Furthermore, the data from samples in the U.S. support increasing concentrations of Pt in roadside dust over time with higher Pt and PGE concentrations closer to roads with heavier traffic patterns (Ely et al., 2001; Hodge and Stallard, 1986).

The above information on Pt emissions and environmental levels indicate the potential for exposure of the general population in the U.S. and Europe to Pt in one or more forms. Because of the increasing use of automobile catalytic converters since the 1970s, there has been some expectation that human exposure to Pt in air may be increasing, particularly for people who spend considerable time in the proximity of roadways. However, several studies of urinary levels of Pt as a marker of Pt exposure have not found consistent correlations between elevated levels of Pt in urine and exposure to traffic (see Benemann et al., 2005; Ravindra et al., 2004; Herr et al., 2003 for review). For example, multiple regression analyses of urinary Pt levels in samples of the German population (people not expected to have occupational exposure to Pt) found that the number of noble metal dental restorations was a significant explanatory variable, whereas traffic-related variables were not (Benemann et al., 2005; Herr et al., 2003). These findings indicate that exposure to Pt through dental alloys currently may be a more significant exposure pathway for the general population than traffic-related exposures. Several other studies have found that nonenvironmental sources of Pt exposure (e.g., dental alloys and Pt from prostheses including breast implants) may confound estimates of true environmental exposures (Maharaj, 2004; Merget et al., 2002). Because Pt can enter into the food chain, there is an expectation that exposure to Pt can also occur through the diet (Jorhem et al., 2008; Frazzoli et al., 2007). A study of Pt levels in the diet of 84 German children indicated that dietary intake of Pt ranged from <0.81 to 32 ng Pt/kg-bw/week, with a median value of 2.3 ng Pt/kg-bw/week (Wittsiepe et al., 2003). The daily intake estimates for children in the Wittsiepe et al. (2003) study of German diets (about 0.33 ng Pt/kg-bw/day) were lower than daily estimates for adults in dietary intake studies of adults in the U.K. (2.9 ng Pt/kg-bw/day; Ysart et al., 1999) and Australia

(20.1 ng Pt/kg-bw/day; Vaughan and Florence, 1992). Data on dietary levels of Pt for adults or children in the U.S. were not located.

Bioavailability of Pt in the Environment

Although Pt and other PGEs in automobile exhaust are expected to be predominantly in water-insoluble metallic or oxide forms, there is evidence that environmental transformation to more soluble forms can occur to a limited extent via oxidation by organic materials in sediments or soils such as humic acids, a transformation that may be enhanced due to the ultrafine nature of the emitted particles (Sures and Zimmermann, 2007; Ravindra et al., 2004). Conjugation to microbially produced ligands (siderophores) may enhance the bioavailability and increase the mobility of Pt compounds in the environment (Dahleimer et al., 2007). Transformation to more soluble forms is expected to increase the bioavailability of Pt. Uptake of Pt and other PGEs by plants and aquatic organisms has been demonstrated; thus, entry of Pt into the food chain is expected to some extent (e.g., Hooda et al., 2008; Sures and Zimmermann, 2007; Ek et al., 2004; Ravindra et al., 2004). Although these studies demonstrate post-depositional transformation of Pt and clear PGE uptake, there are no speciation data on environmental Pt in these studies to identify the Pt compounds associated with greater bioavailability. Two recent in vitro studies (Colombo et al., 2008a, b) have compared bioavailability of Pt in road dust to the bioavailability of powdered automobile catalyst using artificial digestive and lung fluids (see Section 3.1.1 and 3.1.2 for complete study details). Colombo et al. (2008a, b) report that Pt in roadside dust is 7–50 times more bioavailable than Pt from the powdered automobile catalysts. However, no speciation data are available to identify the particular Pt compounds that were more bioavailable.

3. TOXICOKINETICS

Toxicokinetic data are available for a number of soluble Pt compounds (principally $Pt[SO_4]_2$, the halogenated Pt salts $PtCl_4$, $(NH_4)_2PtCl_6$, and K_2PtCl_4) and insoluble Pt compounds (Pt metal, PtO_2, and $PtCl_2$). As discussed in detail in Chapter 2, measurements of soluble Pt are obtained using quantitative techniques after extracting samples into a solution (e.g., water, dilute hydrochloric acid, or nitric acid). Therefore, soluble Pt is an operationally-defined fraction of Pt in which many different species of Pt can be present depending on the extraction solution. Reported estimates of oral absorption of insoluble Pt metal (Pt-Al_2O_3 complex) or soluble Pt such as the halogenated Pt salt $PtCl_4$ are <1% of the dose (Artelt et al., 1999a; Moore et al., 1975b, c). Inhaled soluble and insoluble Pt compounds are cleared from the respiratory tract by mucociliary transport and absorption (Moore et al., 1975a). Soluble $Pt(SO_4)_2$ is cleared from the lung more rapidly than insoluble Pt metal and PtO_2, suggesting greater absorption of soluble Pt compounds such as $Pt(SO_4)_2$ (Moore et al., 1975a). A consistent pattern of tissue distribution of Pt (i.e., highest concentrations in kidney, liver, spleen) was observed following absorption of soluble (e.g., $Pt[SO_4]_2$ or the halogenated Pt salts $PtCl_4$, Na_2PtCl_6) and insoluble (e.g., Pt metal, $PtCl_2$, Pt-Al_2O_3 complex) Pt compounds (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975). Parenteral studies with $PtCl_4$ indicate that Pt accumulates in the fetus (Moore et al., 1975a, b), suggesting that Pt is transported across the placenta for at least one soluble Pt compound. Fecal excretion of unabsorbed Pt is the dominant excretory pathway for ingested soluble and insoluble Pt compounds (Artelt et al., 1999a; Moore et al., 1975a, b, c). Absorbed Pt is excreted in feces and urine (Moore et al., 1975b, c). Inhaled soluble Pt forms ($Pt[SO_4]_2$ and the halogenated Pt salt $PtCl_4$) are excreted from the body more rapidly than insoluble Pt forms (PtO_2, Pt metal); however, slower excretion of insoluble forms may, in part, reflect slower clearance from the lung.

3.1. ABSORPTION

3.1.1. Oral

Absorption of dietary Pt was estimated in a study of 21 Australians in which Pt levels were reported for hair, blood, urine, and feces (Vaughan and Florence, 1992). The study also analyzed total Pt content in a variety of foods obtained from a 1986 Market Basket Survey after the foods had been prepared by normally prepared cooking processes. For both dietary and human samples, Pt concentrations were determined by adsorptive voltammetry (limit of detection [LOD] not reported) and speciation or identification of individual Pt compounds was not reported. The reported mean concentrations of Pt in hair, blood, urine, and feces were 4.90 ± 4.76 µg/kg tissue, 0.60 ± 0.39 µg/L, 0.25 ± 0.25 µg/L, and 8.65 ± 5.13 µg/kg, respectively. Concentrations of Pt in urine showed the widest variation with a 46-fold range (0.02–0.92 µg/L)

that is only slightly reduced when normalized to creatinine concentration to correct for dilution (0.03–0.82 μg/g creatinine). The authors estimated the daily intake of 1.44 μg Pt/day (20.6 ng Pt/kg-bw/day) using a hypothetical diet and their measurements of Pt concentrations in food (ranging from 8.11 μg/kg for liver to 0.13 μg/kg for full-cream milk). Using the 20.6 ng Pt/kg-bw/day dietary estimate, and the concentration of Pt excreted in urine, the authors estimated that 42–60% of the dietary Pt was absorbed (Vaughan and Florence, 1992). Other quantitative estimates of amounts and rates of gastrointestinal (GI) absorption of Pt compounds in humans have not been reported. The Vaughan and Florence (1992) estimate is approximately 50 times the Pt absorption measured in rodents, and the authors suggest that the higher relative absorption may reflect the greater bioavailability of the Pt found in dietary sources. The absorption estimate is based on dietary estimates based on a hypothetical diet, and the authors note that human absorption measurements from subjects receiving diets with known Pt concentrations is required to make more reliable conclusions on absorption.

Colombo et al. (2008a, b) used a physiologically based extraction test with artificial digestive and lung fluids to study the potential human uptake of PGEs from roadside dust in vitro (the artificial lung fluid results are described below in Section 3.1.2 Inhalation). Material analyzed included: (1) a Certified Reference Material sample of road dust with a maximum particle size of 90 μm from the Institute of Reference Materials and Measurements; (2) powdered automobile catalyst with maximum particle size of 74 μm from the National Institute of Standards and Technology (NIST); and (3) PGE-hydroxides for Pt, palladium, and rhodium ($Pt[OH]_2$, $Pd[OH]_2$, $Rh[OH]_3$) mixed 4:88 with alumina powder to simulate PGEs released from catalysts. Bioavailability in the digestive tract was estimated with the use of a physiologically based extraction test performed in two phases to simulate the passage of material through the acid conditions of the stomach and the near-neutral conditions of the small intestine (Colombo et al., 2008a). Concentrations of PGEs in these environmental samples before and after the physiologically based extraction test were determined by ICP-MS. The percent of Pt that is bioavailable in the reference sample of road dust was estimated at 15.5–17% based on the results of the physiologically based extraction test (Colombo et al., 2008a). In contrast, the authors reported that 0.1–0.3% of the Pt from powdered catalyst and 0.01% of the Pt from the simulated PGE released from automobile catalyst was bioavailable. The authors suggest that PGEs in road dust are likely to have been transformed to more soluble compounds in the environment; however, the study did not include characterization of individual Pt compounds.

Studies in rats indicate that only a very small fraction of the administered oral dose of $PtCl_4$, a soluble halogenated Pt salt, is absorbed. Moore et al. (1975b, c) administered a gavage dose of tracer amounts of [$^{191,193}PtCl_4$] to male CD-1 rats (n = 20) and measured whole-body retention kinetics by whole-body counting of [^{191}Pt] gamma activity for 28 days following dosing. Whole-body retention exhibited approximately bi-phasic, first-order kinetics, with an initial rapid phase that coincided with relatively high rates of fecal excretion of Pt (contributed

by excretion of unabsorbed Pt). Based on extrapolation of the terminal phase of whole-body retention kinetics to the time of dosing (this phase would be expected to be minimally influenced by excretion of unabsorbed Pt), absorption was estimated to have been <1% of the administered dose (this value presumably represents a group mean; SD was not reported).

Artelt et al. (1999a) administered a gavage dose of a suspension of Pt-coated Al_2O_3 particles to female Lewis rats (n = 8) and measured amounts of Pt recovered in tissues and urine 8 days following the Pt dose. The Pt-coated particles were produced to be similar to Pt particulates emitted from automobile exhaust catalytic converters, which consist of ultrafine Pt metal complexed to Al_2O_3 particles. The Pt-Al_2O_3 particles were produced by adsorbing H_2PtCl_6 onto Al_2O_3 powder (≤5 μm particle size), followed by calcinating (at 473–737°K) in the presence of oxygen, followed by reduction in hydrogen. The resulting complex had a Pt content of approximately 3.1% (w/w). The solubility of Pt in the complex was approximately 0.4% in distilled water and 10% in 0.9% NaCl (i.e., isotonic). The Pt dose administered to the animals was 1,030 μg Pt (contained in 33.3 mg of the Pt-Al_2O_3 complex). Pt concentrations in tissues and urine (collected in metabolic cages) were measured by atomic absorption spectrometry (AAS) (LOD = 0.5 μg/g tissue; limit of quantitation [LOQ] = 1 μg/g tissue) and/or ICP-MS (LOD = 7.5 ng/g tissue; LOQ = 15 ng/g tissue). Based on recovery of Pt in tissues (blood, femur, kidney, liver, lung, spleen, washed GI tract) 8 days following the dose and cumulative excretion, absorbed Pt was estimated to have been approximately 0.11% of the administered dose (this value presumably represents a group mean; SD was not reported).

Detection of Pt in kidney and other tissues following oral exposures to Pt compounds provides additional evidence for absorption of Pt (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975b, c). These studies are described in greater detail in Section 3.2.1.

The Reichlmayr-Lais et al. (1992) study is particularly pertinent because it directly compared the distribution of Pt following oral exposure to a relatively soluble ($PtCl_4$) or insoluble ($PtCl_2$) Pt compound. Reichlmayr-Lais et al. (1992) exposed male Sprague-Dawley rats (nine rats per dose) to $PtCl_2$ or $PtCl_4$ in the diet (ad libitum) at concentrations of 0, 0.01, 0.05, 0.10, 0.5, 1.0, 5.0, 10, or 50 mg Pt/kg diet for 4 weeks. The corresponding group mean Pt intakes (SD not reported), determined from measurements of food consumption, were 0, 0.004, 0.021, 0.041, 0.21, 0.42, 2.0, 4.0, and 21 mg Pt/animal in animals exposed to $PtCl_2$ and 0, 0.004, 0.020, 0.040, 0.21, 0.41, 2.0, 4.1, and 21 mg Pt/animal in animals exposed to $PtCl_4$. Pt concentrations (mg/kg tissue dry weight) in various tissues (adipose, brain, femur, heart, kidney, liver, muscle, plasma, spleen, testes, carcass) were measured at the conclusion of exposure by AAS (LOD was not reported). The highest tissue concentrations of Pt were found in kidney, which increased with increasing Pt dose. Concentrations in kidneys of animals exposed to $PtCl_2$ or $PtCl_4$ were similar; the group mean concentration ratios ($PtCl_2$:$PtCl_4$) for the five exposure groups for which concentrations were reported (0.5, 1, 5, 10, and 50 mg Pt/kg diet) were 1.4, 1.5,

0.73, 0.75, and 0.81. These results provide supporting evidence of absorption of Pt during exposures to $PtCl_2$ or $PtCl_4$ in the diet. Although quantitative estimates of the fractions of the dose absorbed were not reported, the comparison of Pt levels in kidney suggests that absorption of soluble $PtCl_4$ and relatively insoluble $PtCl_2$ were similar.

In summary, results of the Moore et al. (1975b, c) study suggest that oral absorption of the water-soluble Pt compound, $PtCl_4$, is <1% of the administered dose. Results from the Artelt et al. (1999a) study suggest that absorption of an oral dose of a Pt-Al_2O_3 complex was approximately 0.11% of the Pt dose. The Pt solubility of this complex in isotonic sodium chloride solution was approximately 10% (Artelt et al., 1999a). Based on these limited observations, oral absorption of both soluble and insoluble Pt compounds may be <1% of an administered dose. Similar tissue concentrations observed in rats following similar oral doses of relatively soluble ($PtCl_4$) or insoluble ($PtCl_2$) Pt compounds also suggest that solubility did not substantially affect absorption (Reichlmayr-Lais et al., 1992).

3.1.2. Inhalation

Quantitative studies of amounts and rates of absorption of inhaled Pt compounds in humans have not been reported. Colombo et al. (2008a, b) used a physiologically based extraction test with artificial digestive and lung fluids to study the potential human uptake of PGEs from roadside dust in vitro (the artificial digestive fluid results are described above in Section 3.1.1 Oral). Material analyzed included: (1) a Certified Reference Material sample of road dust with a maximum particle size of 90 μm from the Institute of Reference Materials and Measurements; (2) powdered automobile catalyst with maximum particle size of 74 μm from the NIST; and (3) PGE-hydroxides for Pt, palladium, and rhodium ($Pt[OH]_2$, $Pd[OH]_2$, $Rh[OH]_3$) mixed 4:88 with alumina powder to simulate PGEs released from catalysts. In Colombo et al. (2008b), bioavailability in the lung was estimated with the use of two simulated lung fluids in vitro: (1) Gamble's solution representative of interstitial fluid of the deep lung, and (2) artificial lysosomal fluid representative of more acidic environment in the lung. The percent of Pt that was dissolved, and therefore bioavailable, in the reference sample of road dust was estimated at approximately 36% in the artificial lysosomal fluid (Colombo et al., 2008b). In contrast, the percentage of Pt from powdered catalyst and the simulated PGE released from automobile catalyst in the artificial lysosomal fluid was <5% bioavailable (data from Figure 2 in Colombo et al., 2008b). The bioavailability in the higher pH (7.4) Gamble's solution was considerably lower (<0.5%) compared to the lower pH (4.5) artificial lysosomal fluid for all the PGEs. The authors suggest that Pt compounds in road dust are likely to have been transformed to more soluble compounds in the environment; however, the study did not include characterization of individual Pt compounds

As is generally the case for inhaled particulates, absorption of inhaled aerosols of Pt compounds that are deposited in the respiratory tract are expected to be influenced by size of the

inhaled particles and solubility as well as the size-dependent pattern of regional deposition within the respiratory tract (Bailey and Roy, 1994; James et al., 1994). Fine particles (<1 μm) deposited in the bronchiolar and alveolar region can be absorbed after extracellular dissolution or may be ingested by phagocytic cells and transported from the respiratory tract. Larger particles (>2.5 μm) that are deposited, primarily, in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Studies in animals have observed retention kinetics of inhaled Pt aerosols typical of mucociliary clearance of particles from the respiratory tract, combined with absorption of particles deposited in the deeper regions of the respiratory tract. For example, Moore et al. (1975a) exposed CD-1 rats (81 animals per compound, sex not reported), nose-only for 48 minutes, to aerosols of [^{191,193}Pt] as insoluble PtO_2 (7–8 mg/m^3) or Pt metal (7–8 mg/m^3), or as soluble $PtCl_4$ (5 mg/m^3) or $Pt(SO_4)_2$ (5–6 mg/m^3). The aerodynamic diameter of the particulate aerosols was reported as "nearly 1.0 μm" (this value appears to have been calculated based on the nebulizer droplet size and concentration of the nebulizing solution). Whole body retention kinetics of [^{191}Pt] were measured by whole-body counting of [^{191}Pt] gamma activity for up to 20 days following exposure. Fast and slow phases of whole-body retention kinetics of Pt were evident for all four Pt compounds (see Section 3.4.2). The fast phase occurred during the first 24 hours following exposure and coincided with the appearance of relatively large amounts of Pt in feces (relative to urine) indicative of mucociliary clearance of Pt initially deposited in the respiratory tract. Initial lung burdens were reported as 14% of initial body burden (coefficient of variation [CV] = 34%) following exposure to Pt metal and 16% (CV = 30%) of initial body burden following exposure to PtO_2 (initial lung burdens for other Pt compounds were not reported). During the fast phase of elimination, approximately 37% of the initial lung burden was eliminated from the lung following exposure to Pt metal. The corresponding fast phase elimination was 43% following exposure to PtO_2 and 26% following exposure to $Pt(SO_4)_2$ (these values presumably represent group means; values for SD were not reported). Pseudo-first-order elimination half-times of Pt from the lung for the slow phase were approximately as follows: Pt metal, 19 days; PtO_2, 8 days; and $Pt(SO_4)_2$, 4 days. These estimates are based on reported data on lung retention for the period 2–16 days postexposure reported in Table 1 of Moore et al. (1975a); data for $PtCl_4$ were not reported. The above half-times suggest that soluble $Pt(SO_4)_2$ was cleared from the lung more rapidly than the less-soluble Pt metal or PtO_2.

Artelt et al. (1999a) exposed female Lewis rats (four animals/dose) to aerosols of a Pt-Al_2O_3 complex (see Section 3.1.1 for more detailed description of study) having a mass median aerodynamic diameter (MMAD) of 1.3 μm (geometric standard deviation [GSD] not reported), and Pt content of 2.7%. The exposure was nose-only, 5 hours/day, 5 days/week for 13 weeks to 4 or 12 mg/m^3 of the Pt-Al_2O_3 aerosol (approximately 0.1 or 0.3 mg Pt/m^3). Urine and fecal Pt were measured 3 times during the exposure, and Pt in tissues (adrenals, blood, bronchial lavage fluid and cells, femur, kidney, liver, lung, spleen, stomach) was measured at the

conclusion of the 90-day exposure. Pt in tissues and excreta were measured by ICP-MS (LOD = 7.5 ng/g tissue; LOQ = 15 ng/g tissue). The estimated mean total amounts of Pt recovered in all tissues (including lung) and excreta were 776 and 1,390 μg in animals exposed to 0.1 or 0.3 μg Pt/m^3, respectively. These represent estimates of the total amounts of Pt deposited in the respiratory tract during the exposure. Of these amounts, Pt in feces amounted to approximately 98%; and approximately 1% was recovered in lung, and 1% was recovered in urine and tissues other than lung. The mean amount of Pt in lung at the conclusion of the study was 5.19 μg (SD = 0.48, approximately 0.67% of total) and 17.8 μg (SD = 2.8, approximately 1.3% of total) in animals exposed to 0.1 or 0.3 mg Pt/m^3, respectively. Pt bioavailability was estimated as the total amount of Pt recovered in bone, kidney, liver, spleen, stomach, and urine, expressed as a fraction of the body burden (i.e., sum of tissues, urine plus lung). Estimated mean bioavailability percentages were 31.4 and 22.7% (SD not reported) in the animals exposed to 0.1 or 0.3 mg Pt/m^3, respectively. Since absorbed Pt may have been excreted in feces (Artelt et al., 1999a; Moore et al., 1975b, c), this represents a minimum estimate of the fraction of the body burden that had been absorbed.

In summary, based on the results of the Moore et al. (1975a) rat study, following inhalation of soluble and relatively insoluble forms of Pt aerosols (approximately 1 μm particle size), Pt deposited in the lung was eliminated from the lung by mucociliary clearance to the GI tract and by absorption from the lung. Based on measurements of lung clearance kinetics during days 2–16 after exposure (i.e., beyond the early mucociliary clearance phase of elimination), soluble $Pt(SO_4)_2$ appeared to be absorbed more rapidly from the lung than the less-soluble forms, Pt metal and PtO_2. The Artelt et al. (1999a) study provides a quantitative estimate of the total amount of Pt deposited in the lung and amounts retained in and absorbed from the lung during a 90-day exposure to an aerosol of a Pt-Al_2O_3 complex (approximately 1.3 μm particle size). Of the total amount estimated to have been deposited in the respiratory tract during the exposure, approximately 98% was recovered in feces, approximately 1% was recovered in lung, and 1% was recovered in urine and tissues other than lung.

3.1.3. Dermal

No studies are available that provide information on the absorption of Pt when exposure occurs from dermal contact with environmentally relevant Pt compounds.

3.2. DISTRIBUTION

3.2.1. Oral

The tissue distribution of Pt following oral administration of soluble ($Pt[SO_4]_2$ and the halogenated Pt salt $PtCl_4$) or insoluble ($PtCl_2$ and Pt metal) Pt compounds, localizes primarily to soft tissues, with the highest residual concentrations achieved in kidney, liver, and spleen (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et

al., 1975; Moore et al., 1975a, b). Similar patterns of distribution (i.e., highest concentrations in kidney, liver, spleen) were observed for these four soluble and insoluble Pt compounds.

Reichlmayr-Lais et al. (1992) exposed male Sprague-Dawley rats (nine rats per dose) to $PtCl_2$ or $PtCl_4$ in the diet (ad libitum) at concentrations of 0.5, 1.0, 5.0, 10, or 50 mg Pt/kg diet for 4 weeks. The corresponding group mean Pt intakes (SD not reported), determined from measurements of food consumption, were 0.21, 0.42, 2.0, 4.0, and 21 mg Pt/animal in animals exposed to $PtCl_2$ and 0.21, 0.41, 2.0, 4.1, and 21 mg Pt/animal in animals exposed to $PtCl_4$. Pt concentrations (mg/kg tissue dry weight) in various tissues (adipose, brain, femur, heart, kidney, liver, muscle, plasma, spleen, testicles, carcass) were measured at the conclusion of exposure by AAS (LOD and LOQ not reported). The highest tissue concentrations were found in kidney, which increased with increasing Pt dose. Concentrations in kidneys of animals exposed to $PtCl_2$ or $PtCl_4$ were similar; the group mean concentration ratios ($PtCl_2$:$PtCl_4$) for the five exposure groups for which tissue concentrations were reported (0.5, 1, 5, 10, or 50 mg Pt/kg diet) were 1.4, 1.5, 0.73, 0.75, and 0.81 (calculated from group mean data reported in Tables 4 and 5 of Reichlmayr-Lais et al., 1992). Tissue distribution was also similar in rats exposed to $PtCl_2$ or $PtCl_4$, apparent from comparison of the ratios of the Pt concentration in tissues compared to that of plasma (calculated from group mean data reported in Tables 4 and 5 of Reichlmayr-Lais et al., 1992). For example, tissue:plasma Pt concentration (µg Pt/g dry tissue) ratios in rats exposed to 10 mg Pt/kg diet as $PtCl_2$ were: kidney, 226; liver, 9; spleen, 7; femur, 6.5; skeletal muscle, 3.5; heart, 3.0; and brain, testes, and fat, <1.5. Tissue:plasma Pt concentration (µg Pt/g dry tissue) ratios in rats exposed to 10 mg Pt/kg diet as $PtCl_4$ were: kidney, 300; liver, 15; femur, 12; spleen, 8.5; skeletal muscle, 3.5; brain, 4.5; heart and testes, 3.0; and fat, <1.5. These results suggest that tissue distribution of Pt absorbed during exposures to $PtCl_2$ or $PtCl_4$ in the diet are similar.

The above observations of the kidney having the highest residual concentrations of absorbed Pt following exposure to $PtCl_4$ are consistent with those reported by Moore et al. (1975b, c) in male CD-1 rats described in detail in Section 3.2.1. Following a single oral tracer dose of [$^{191,193}PtCl_4$], [^{191}Pt] gamma activity was detected above background only in kidney and liver (actual concentrations were not reported). Moore et al. (1975c) reported the highest concentrations in kidney following intravenously-administered [$^{191}PtCl_4$] from the same study (see Section 3.2.4).

Holbrook et al. (1975) exposed male Sprague-Dawley rats (2–16 animals per dose) to $Pt(SO_4)_2$ or $PtCl_4$ in drinking water (ad libitum) at concentrations of 106 or 319 mg Pt/L ($Pt[SO_4]_2$), and 319 mg Pt/L ($PtCl_4$). Total Pt doses were reported as 26 or 80 mg Pt/rat during the exposure to $Pt(SO_4)_2$ and 60 mg Pt/rat during the exposure to $PtCl_4$. Concentrations (µg Pt/g wet) of Pt in tissues (blood, brain, heart, kidney, liver, spleen, testes) were determined immediately following 8 or 9 days of exposure. Pt in tissues was measured by emission spectroscopy; the detection limit of this method was reported in Yoakum et al. (1975) as 0.01–

0.05 µg/electrode. The highest concentrations of Pt were in kidney in animals exposed to $Pt(SO_4)_2$ or $PtCl_4$. In animals exposed to $Pt(SO_4)_2$, kidney Pt concentrations (µg Pt/g wet weight) were 0.26 ± 0.05 (SD, n ≥ 4) following exposure to 106 mg Pt/L and 4.5–4.7 µg/g (n = 2) following exposure to 319 µg Pt/L. The latter kidney concentrations were similar to that observed in animals exposed to $PtCl_4$ at a similar dose (60 mg Pt/rat as $PtCl_4$, compared to 80 mg Pt/rat as $Pt[SO_4]_2$): 4.8 ± 0.5 µg/g (SD, n ≥ 4). Tissue:blood Pt concentration (µg Pt/g wet tissue) ratios in animals exposed to 106 mg Pt/L of $Pt(SO_4)_2$ (25 mg Pt/rat) were as follows (calculated from group mean data reported in Table 4 of Holbrook et al., 1975): kidney, 5; liver, 1; testes, 0.8; spleen, 0.4; heart, 0.4; and brain, not detected. Tissue:blood Pt concentration ratios in animals exposed to 319 mg Pt/L of $Pt(SO_4)_2$ (80 mg Pt/rat) were as follows: kidney, 21; liver, 4; heart, 1; spleen, 0.6; brain, 0.07; and testes, not detected. Tissue:blood Pt concentration ratios in animals exposed to 319 mg Pt/L $PtCl_4$ (60 mg Pt/rat) were as follows: kidney, 21; liver, 10; spleen, 1; and brain, heart, and testes, not detected.

Holbrook et al. (1975) also compared the tissue distributions of Pt in rats following a single gavage dose (382 mg Pt/kg) or intraperitoneal dose (113 mg Pt/kg) of $Pt(SO_4)_2$. Data were obtained from survivors of a 14-day lethality study, and the doses administered were close to the median lethal dose (LD_{50}). The highest Pt concentration following the oral dose was in kidney. Tissue:blood Pt concentration (µg Pt/g wet tissue) ratios in animals exposed to the oral dose of $Pt(SO_4)_2$ were as follows (calculated from group mean data reported in Table 5 of Holbrook et al., 1975): kidney, 5; spleen, 1; liver, 0.7; heart, 0.3; testes, 0.15; and brain, 0.03. Concentrations of Pt in liver were substantially higher following the intraperitoneal dose; tissue:blood Pt concentration ratios were as follows: kidney, 37; liver, 34; spleen, 16; heart, 3; testes, 1; and brain, 0.6.

Lown et al. (1980; Massaro et al., 1981) reported tissue concentrations in male Swiss mice at various times following single or repeated doses of $Pt(SO_4)_2$. In the single-dose study, mice (40 animals/dose) received a gavage dose of 144 or 213 mg Pt/kg (7-day LD_{05} and LD_{25}, respectively). Pt concentrations (µg/g wet weight) in tissues (blood, brain [cerebellum, cerebrum, brain stem], kidney, liver, lung, muscle, spleen, testes) were determined on 10 animals at 4 hours, 1 day, 3 days, and 7 days following the dose. Tissue Pt concentrations were measured by AAS (detection limits were not reported). The highest concentrations in tissues were observed in kidney, liver, spleen, and lung. For example, 3 days following the 144 mg Pt/kg dose, tissue:blood concentration ratios were approximately: kidney, 3.0; liver, 2.3; spleen, 1.4; lung, 0.9; and other tissues (testes, muscle, brain), <0.3. In animals that received the 213 mg Pt/kg dose, tissue:blood concentration ratios on day 3 were approximately: kidney, 1.4; liver, 2.6; spleen, 1.3; lung, 0.6; and other tissues (testes, muscle, brain), <0.3. In the repeated-dose study, mice (n = 100) received gavage doses of 109 mg Pt/kg as $Pt(SO_4)_2$ (7-day LD_{01}) every 3 days for a total of 10 doses (Lown et al., 1980). A subset of the mice were sacrificed (n = 10) 3 days following 2, 4, 6, 8, or 10 doses, and tissue Pt concentrations were determined. Three

days following 10 daily doses of 109 mg Pt/kg, tissue:blood concentration ratios were: kidney, 8; lung, 8; spleen, 2; liver, 0.9; and testes, 0.5.

Artelt et al. (1999a) reported Pt levels in various tissues in female Lewis rats (n = 80), following a single gavage dose of Pt metal (1,030 μg Pt), administered as a particulate suspension of Pt-Al_2O_3 complex (see Section 3.1.1 for detailed description of this study). The highest concentrations (μg/g wet tissue) were observed in kidney (0.08 ± 0.02 SD), spleen (0.0056 ± 0.0013 SD), liver (0.0035 ± 0.0008 SD), and lung (0.0022 ± 0.0005 SD). Tissue:blood Pt concentration ratios were approximately: kidney, 5; spleen, 0.4; lung, 1.4; and liver, 0.2 (calculated from group means reported in Table 12 of Artelt et al., 1999a). Artelt et al. (1999a) also reported urinary and fecal excretion of Pt following intravenous administration of K_2PtCl_4; this study is summarized in the discussion of Pt excretion (see Section 3.4.4).

In summary, the tissue distribution of Pt absorbed following oral administration appears to be similar for soluble and less-soluble compounds, based on the results of studies conducted on relatively soluble compounds of Pt ($PtCl_4$, $Pt[SO_4]_2$) and less soluble compounds ($PtCl_2$, Pt-Al_2O_3 complex) (Artelt et al., 1999a; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975b, c). The highest tissue concentrations are observed in kidney, liver, spleen, and lung. Pt concentrations in kidney were 5–20 times that of liver. Although most studies have been conducted in rats, the results of one oral study in the mouse also found the highest concentrations of Pt in kidney, liver, spleen, and lungs (Lown et al., 1980). Following intravenous administration of soluble $PtCl_4$ to rats, the highest concentrations of Pt were also observed in kidney (Moore et al., 1975c). A direct comparison of the distribution of tissue distributions of Pt in rats following a single gavage dose (382 mg Pt/kg) or intraperitoneal dose (113 mg Pt/kg) of $Pt(SO_4)_2$ showed substantially higher concentrations of Pt in liver (relative to blood) following the intraperitoneal dose, compared to the oral dose (Holbrook et al., 1975).

3.2.2. Inhalation

Quantitative studies of the tissue distribution of inhaled Pt in humans have not been reported. Tissue distribution of Pt following exposures to aerosols of Pt metal or as a Pt-Al_2O_3 complex has been studied in CD-1 Lewis rats (Artelt et al., 1999a; Moore et al., 1975a). Moore et al. (1975a) determined tissue distribution of Pt in CD-1 rats (n = 87, sex not reported), following 48-minute nose-only exposures to an aerosol of [^{191,193}Pt] as insoluble Pt metal (7–8 mg/m^3). The aerodynamic diameter of the particulate aerosol was reported as "nearly 1.0 μm" (see Section 3.1.2 for a more complete description of this study). The highest Pt concentrations (based on [^{191}Pt] gamma activity) were found in the respiratory tract, kidney, and bone (data comparing tissue distribution of soluble and insoluble forms were not reported). Tissue:blood concentration ratios 8 days following the exposure were: lung, 2,000; kidney, 69; bone, 13; liver, 1.4; and brain, heart, muscle, and spleen, <0.5. Although the Moore et al. (1975a) study

also exposed rats to aerosols of $PtCl_4$, PtO_2, or $Pt(SO_4)_2$, tissue distribution was reported only for animals exposed to Pt metal.

Artelt et al. (1999a) exposed female Lewis rats (four animals/dose) to aerosols of Pt metal bound to aluminum oxide particles (MMAD: 1.3 μm) and observed the highest amounts of Pt in lung, kidney, and liver (see Section 3.1.2 for a more complete description of this study). The exposure was nose-only 5 hours/day, 5 days/week for 13 weeks to 4 or 12 mg/m^3 of the Pt-Al_2O_3 aerosol (approximately 0.1 or 0.3 mg Pt/m^3). At the conclusion of exposure to 12 mg/m^3 of the Al_2O_3/Pt aerosol (approximately 0.3 mg Pt/m^3), the tissue:blood Pt levels (μg/organ or tissue) were as follows (calculated from group mean data reported in Table 8 of Artelt et al., 1999a): lung, 214; liver, 1.6; kidney, 0.5; spleen, 0.07; and femur, 0.07. Assuming relative masses (percent of body weight) of liver (4%), kidney (0.8%), lung (0.6%), and blood (5%) in the rat (Davies and Morris, 1993), corresponding tissue:blood Pt concentration ratios were approximately: lung, 1,900; kidney, 3.4; and liver, 2.1. Similar tissue:blood ratios were observed after intratracheal instillation of Al_2O_3/Pt particulate suspensions (Artelt et al., 1999a).

Ultrafine particles (diameters <0.1 μm) of insoluble materials can contribute very little to the overall mass of airborne PM in urban air, but at low gravimetric concentrations (less than about 125 μg/m^3) when aggregation is impeded, large numbers of ultrafine particles can exist (Oberdörster, 2001). The only published information on the tissue distribution inhaled ultrafine Pt particles is a report of an experiment examining the Pt content of different tissues in one male F344 rat sacrificed 0.5 hours after a 6-hour exposure to ultrafine particles (count median diameter = 13 nm; GSD = 1.7) of Pt metal at a concentration of about 110 μg/m^3 (Oberdörster, 2001; Oberdörster et al., 2000). Pt content in tissues was determined by ICP-MS (LOD reported as 10 pg/g tissue) and expressed as a percentage of the total Pt detected in several tissues (lungs, blood, trachea, liver, and kidney). Tissue:blood Pt concentrations ratios were: lung, 10,000; liver, 77; and kidney, 3 (based on data from Table 7 of Oberdörster, 2001). The results demonstrated that Pt was transported to the liver, but it is uncertain if the particles themselves were transported or if some of the particles were dissolved in the lung before transport of Pt to the liver. Direct comparisons of the disposition of ultrafine and larger-sized particles of Pt following inhalation exposure are not available.

The localized distribution of Pt within tissues and cells is largely unknown. In female Lewis rats, following intratracheal administration of Pt metal, administered as a particulate suspension of a Pt-Al_2O_3 complex, approximately 2–5% of Pt in plasma was associated with complexes of molecular weight <60 kDa, the remaining fraction was associated with higher molecular weight complexes (Artelt et al., 1999a). When rat plasma was incubated with K_2PtCl_4, high molecular weight complexes ranging from 60 to 900 kDa were observed. A relatively large complex in the 63–83 kDa range may have included serum albumin. High molecular weight complexes (>63 kDa) were also the dominant complexes found in lung tissue

and bronchiolar lavage cells, following intratracheal administration of Pt metal (suspension of Pt-Al_2O_3 complex) to female Lewis rats (Artelt et al., 1999a).

In summary, based on the results of studies conducted in rats on relatively insoluble Pt metal (Moore et al., 1975a) and a Pt-Al_2O_3 complex (Artelt et al., 1999a), inhaled Pt deposits in the respiratory tract, undergoes mucociliary clearance to the GI tract, and is absorbed into blood. Pt absorbed from the lung distributes primarily to kidney, liver, and bone. Concentrations of Pt in kidney were approximately 40 times greater than in liver of rats, following an inhalation exposure to Pt metal (Moore et al., 1975a). The above observations pertain to particles of approximately 1 μm in size. Following exposure to ultrafine particles (e.g., 13 nm) of Pt metal, the Pt concentration in liver was 30 times that of the kidney (Oberdörster, 2001; Oberdörster et al., 2000). Although limited to a single observation made in one rat, these results suggest that the tissue distribution of inhaled ultrafine particles of Pt metal may not be predicted from the observed distribution of large (e.g., 1 μm) particles.

3.2.3. Dermal

No studies are available that provide information on the distribution of Pt when exposure occurs from dermal contact with Pt compounds.

3.2.4. Other Routes

Studies of tissue distribution of Pt following parenteral dosing of rats with $PtCl_4$ or $Pt(SO_4)_2$ indicate that absorbed Pt distributes primarily to soft tissues, with the highest concentrations achieved in kidney, liver, and spleen (Holbrook et al., 1975; Moore et al., 1975c, b; Durbin, 1960). Tissue:blood concentrations 7 days after a tracer intravenous dose of [$^{191,193}PtCl_4$] administered to CD-1 rats were: kidney, 11; spleen, 4; adrenal, 2; liver, 2; pancreas, 1.3; bone, 0.7; fat, 0.25; and brain, 0.04 (Moore et al., 1975b, c). Holbrook et al. (1975) compared tissue distributions of Pt in male Sprague-Dawley rats following a single gavage dose (382 mg Pt/kg) or intraperitoneal dose (113 mg Pt/kg) of $Pt(SO_4)_2$. Data were obtained from survivors of a 14-day lethality study and the doses administered were close to the LD_{50}. The highest Pt concentration was in kidney following the oral dose. Tissue:blood Pt concentration (μg Pt/g wet tissue) ratios in animals exposed to the oral dose of $Pt(SO_4)_2$ were as follows (calculated from group mean data reported in Table 5 of Holbrook et al., 1975): kidney, 5; spleen, 1; liver, 0.7; heart, 0.3; testes, 0.15; and brain, 0.03. Concentrations of Pt in liver were substantially higher following the intraperitoneal dose; tissue:blood Pt concentration ratios were as follows: kidney, 37; liver, 34; spleen, 16; heart, 3; testes, 1; and brain, 0.6.

Maternal-fetal transfer of intravenously-administered Pt has been studied in rats. Following an intravenous tracer dose of $^{191}PtCl_4$ administered on day 18 of gestation, the fetus:maternal blood ratio was 0.03 (Moore et al., 1975b, c). From this same study, maternal tissue:blood ratios were: kidney, 12; liver, 4, placenta, 2.6; and ovary, 1.4.

In summary, tissue distribution of absorbed Pt following intravenous injection of soluble $PtCl_4$ in the rat was similar to that observed following oral or inhalation exposures, with the highest tissue concentrations (outside of the lung and GI tract) observed in kidney, liver, and spleen (Moore et al., 1975b, c). A direct comparison of the distribution of tissue distributions of Pt in rats following a single gavage dose or intraperitoneal dose of $Pt(SO_4)_2$ showed substantially higher concentrations of Pt in liver (relative to blood) following the intraperitoneal dose, compared to the oral dose (Holbrook et al., 1975).

3.3. METABOLISM

As an element, Pt is neither created nor destroyed within the body; however, Pt compounds (e.g., $PtCl_4$) can participate in chemical reactions such as hydrolysis, ligand exchange, and formation of revisible and covalent complexes with amino acids, peptides, and nucleic acids. Pt forms complexes with amino, carboxyl, imidazole (e.g., histidine), and sulfhydryl (e.g., cysteine) groups on amino acids (NAS, 1977). As a result, Pt can form complexes with proteins, nucleic acids, and free amino acids. In rats, high (>60 kDa) and low (<60 kDa) weight complexes of Pt have been observed in plasma and lung tissue or rats, following intratracheal administration of a suspension of Pt-Al_2O_3 complex (Artelt et al., 1999a, see Section 3.2.2). Absorbed Pt compounds may participate in redox reactions; however, experimental evidence of this for environmental forms of Pt was not located. Although there is evidence suggesting limited environmental transformation of metallic Pt within soil (Sures and Zimmerman, 2007; Ravindra et al., 2004), data on the potential for transformation of metallic Pt within experimental animals or humans were not located.

3.4. ELIMINATION

3.4.1. Oral

Studies of the routes or kinetics of elimination of Pt in humans following oral exposure to Pt compounds have not been reported. Studies in rodents have shown that absorbed Pt is excreted in feces and urine (see Section 3.4.4 for a discussion of intravenous studies). Oral absorption of Pt administered as $PtCl_4$ or a Pt-Al_2O_3 complex has been estimated to be <1% (Artelt et al., 1999a; Moore et al., 1975b, c; see Section 3.1.1 for more detailed description of these studies). As a result, during the first 1–2 days following ingestion of these Pt compounds, fecal excretion of unabsorbed Pt is likely to contribute substantially to Pt excretion. Absorbed Pt is also excreted in feces. Evidence for this derives from studies of intravenously administered $PtCl_4$ and Pt-Al_2O_3 complex (Artelt et al., 1999a; Moore et al., 1975c; see Section 3.4.4 for more complete description of these studies).

Rates of elimination of orally administered $PtCl_4$ or $Pt(SO_4)_2$ have been measured in mice and rats. Lown et al. (1980; Massaro et al., 1981) reported tissue concentrations in male Swiss mice at various times, up to 7 days following a single dose of $Pt(SO_4)_2$. Elimination half-times

estimated from data for mice that received 144 mg Pt/kg were: blood, 3.3 days; kidney, 2.2 days; and liver, 2.1 days. Moore et al. (1975b, c) measured whole-body retention profiles of Pt in male CD-1 rats, following single oral tracer doses of [$^{191,193}PtCl_4$]. Less than 1% of the oral [^{191}Pt] dose remained in the body 3 days after the dose. Fecal excretion was the dominant excretory pathway during the 11-day observation period; however, the contribution of the urinary pathway increased with time. The urine:feces excretion ratio was approximately 0.01 during the first 2 days following the dose and increased to approximately 0.2 on day 8 following the dose (calculated from data presented in Figure 6 of Moore et al., 1975b). Moore et al. (1975b, c) also reported data on whole-body elimination and excretion of Pt following an intravenous tracer dose of [$^{191,193}PtCl_4$] and observed a much larger contribution of the urinary pathway to excretion (i.e., urine:fecal ratio of 1–2.5; see Section 3.4.4. for a more detailed description of this study). These observations suggest that Pt excreted in feces following the oral dose of $PtCl_4$ derived from both unabsorbed Pt and absorbed Pt.

Artelt et al. (1999a) administered a gavage dose of a suspension of Pt-coated Al_2O_3 particles to female Lewis rats (n = 8) and measured amounts of Pt recovered in tissues and urine 8 days following the Pt dose (see Section 3.1.1 for more detailed description of the study). The Pt dose administered to the animals was 1,030 µg (33.3 mg of the Pt-Al_2O_3 complex). Most of the administered Pt was excreted during the first 24 hours following the dose. Fecal excretion was the dominant pathway; urine:fecal ratios were approximately 0.001 (based on data presented in Figures 5 and 6 of Artelt et al., 1999a).

3.4.2. Inhalation

Schierl et al. (1998) measured urinary Pt excretion in two male Pt refinery and catalyst production workers who were subject to a single 4-hour exposure to estimated concentrations of approximately 1.7 µg Pt/m^3 (Subject A) or 0.15 µg Pt/m^3 (Subject B). Schierl et al. (1998) report that exposure was predominantly to $(NH_4)_2PtCl_6$ by handling dry powder; however, no Pt speciation or exposure measurements were reported. Urinary Pt (ng Pt/g creatinine) was measured for the first 4 days following the exposure and periodically for the subsequent 6 months. Pt content in all samples (urine or air) was quantified by adsorptive voltammetry (LOD was reported to be 2 ng/L urine and 2 pg/m^3 air). Based on these observations, a urinary excretion half-time was estimated to be 50 hours (95% confidence interval [CI]: 36–66). A second, slow elimination component was observed in Subject A; the estimated half-time was 24 days (95% CI: 18–33).

Schierl et al. (1998) also reported urinary Pt levels measured in 34 Pt refinery and catalyst production workers (32 males) who were exposed primarily to K_2PtCl_4 and $Pt(NO_3)_2$. Estimated average exposures based on periodic air sampling were: stationary sampling, 1.2 µg/m^3 (range: 0.2–3.4); and personal sampling, 2.5 µg/m^3 (range: 0.8–7.5). Urinary Pt excretion was 16–6,270 ng/g creatinine among currently exposed workers (n = 18) and 10–

170 ng/g creatinine among workers formerly exposed (exposure ceased 2–6 years earlier; n = 4), compared to 1–12 ng/g creatinine among a reference control group of workers who were not exposed to Pt (n = 12). The persistence of urinary Pt levels above those of the reference control group, 2–6 years following cessation of exposure, suggests the existence of a more slowly eliminated fraction of body burden that may not be reflected in the above elimination half-time estimates.

Rates of elimination of soluble ($Pt(SO_4)_2$, or the halogenated Pt salt $PtCl_4$) and insoluble (Pt metal and PtO_2) Pt compounds have been measured in rats. Moore et al. (1975a) measured the kinetics of whole-body elimination and urinary and fecal excretion in CD-1 rats (n = 87, sex not reported) following 48-minute, nose-only exposures to aerosols of [^{191,193}Pt] as soluble $PtCl_4$ (5 mg/m^3), $Pt(SO_4)_2$ (5–6 mg/m^3), insoluble PtO_2 (7–8 mg/m^3), or Pt metal (7–8 mg/m^3). The aerodynamic diameter of the particulate aerosol was reported as "nearly 1.0 μm". Pt was eliminated in the feces and urine. Fecal excretion was the dominant pathway of excretion during the first 3 days following exposure (indicative of mucociliary clearance of Pt initially deposited in the respiratory tract). Whole-body elimination kinetics exhibited at least two phases: an early fast phase, reflecting mucociliary clearance and fecal excretion of Pt initially deposited in the respiratory tract, followed by a slower phase(s), reflecting excretion of absorbed Pt. The slow phase elimination of Pt was more rapid following inhalation of soluble forms ($PtCl_4$, $Pt[SO_4]_2$) than following inhalation of insoluble forms (PtO_2, Pt metal). The pseudo-first-order elimination half-times for body burden, estimated from data collected after the first 5 days following cessation of exposure were as follows: $PtCl_4$, 9 days; $Pt(SO_4)_2$, 10 days; PtO_2, 44 days; and Pt metal, 32 days (estimated from digitization of Figures 1 and 2 of Moore et al., 1975a). The slower elimination of the insoluble forms may, in part, result from slower clearance from the lung. This is supported by the kinetics of Pt retention in the lung that were observed in this study. Pseudo-first-order elimination half-times of Pt from the lung for the slow phase were approximately as follows: Pt metal, 19 days; PtO_2, 8 days; and $Pt(SO_4)_2$, 4 days (estimates are based on reported data on lung retention for the period 2–16 days postexposure (from Table 1 of Moore et al., 1975a); data for $PtCl_4$ were not reported. The above half-times suggest that soluble $Pt(SO_4)_2$ is cleared from the lung more rapidly than the less-soluble forms of Pt (Pt metal and PtO_2). Fecal excretion was the predominant excretory route for all four Pt compounds; however, the relative contribution of the urinary route increased with time after the inhalation exposure. Urine:fecal excretion ratios for each of the Pt compounds were <0.1 during the first 2 days following exposure and increased to 0.6–0.8 by day 5. These results are consistent with a substantial mucociliary clearance of Pt from the respiratory tract to the GI tract during the first 1–2 days following inhalation exposure. The slow-phase, whole-body elimination half-time of 9 days for Pt inhaled as $PtCl_4$ was similar to the whole-body elimination half-time observed following intratracheal administration of $PtCl_4$, approximately 10 days (Moore et al., 1975b, c).

Artelt et al. (1999a) exposed female Lewis rats (four animals/dose) to aerosols of Pt metal bound to aluminum oxide particles (MMAD: 1.3 μm; see Section 3.1.2 for a more complete description of this study). The exposure was nose-only 5 hours/day, 5 days/week for 13 weeks to 4 or 12 mg/m^3 of the Pt-Al_2O_3 aerosol (approximately 0.1 or 0.3 mg Pt/m^3). Urine and fecal excretion of Pt was determined on days 8, 28, and 90 of exposure. Fecal excretion was the dominant excretory pathway; urine:fecal excretion ratios ranged from 0.002 to 0.004 (based on group mean data reported in Table 9 of Artelt et al., 1999a).

In summary, data on elimination of inhaled Pt compounds in humans are limited to a study of Pt refinery and catalyst production workers (Schierl et al., 1998). This study observed Pt in urine of workers who were exposed predominantly to $(NH_4)_2PtCl_6$ and observed what appeared to be biphasic excretion kinetics with fast- and slow-phase half-times of approximately 50 hours and 24 days, respectively. The study also observed Pt in urine of workers 2–6 years after cessation of exposure primarily to K_2PtCl_4 and $Pt(NO_3)_2$. The persistence of urinary Pt excretion 2–6 years following cessation of exposure suggests the existence of a more slowly eliminated fraction of body burden that may not be reflected in the above elimination half-time estimates. The observation of faster and slower phases of urinary excretion of Pt in humans is consistent with similar observations of multi-phasic elimination of inhaled Pt metal, PtO_2, $PtCl_4$, or $Pt(SO_4)_2$ in rats (Moore et al., 1975a). The pseudo-first-order elimination half-times for the body burden in rats were approximately 9 days for $PtCl_4$, 10 days for $Pt(SO_4)_2$, 44 days for PtO_2, and 32 days for Pt metal (Moore et al., 1975a). The slow-phase urinary excretion half-time estimated for a worker exposed predominantly to $(NH_4)_2PtCl_6$ (24 days; Schierl et al., 1998) falls within this range observed in rats. Studies conducted in rats exposed to aerosols of Pt metal, PtO_2, $PtCl_4$, $Pt(SO_4)_2$, or Pt-Al_2O_3 complex have shown that fecal excretion is the dominant excretory route for these Pt compounds following inhalation exposure; however, the relative contribution of the urinary route increases with time after the inhalation exposure (Artelt et al., 1999a; Moore et al., 1975a). These results are consistent with mucociliary clearance of Pt from the respiratory tract to the GI tract during the first 1–2 days following inhalation exposure. Following this early phase of mucociliary clearance, fecal excretion of absorbed Pt continues to contribute to fecal Pt excretion. Evidence for fecal excretion of absorbed Pt derives from studies of intravenously administered $PtCl_4$ and Pt-Al_2O_3 complex (Artelt et al., 1999a; Moore et al., 1975c; see Section 3.4.4 for more complete description of these studies).

3.4.3. Dermal

No studies are available that provide information on excretion of Pt when exposure occurs from dermal contact with Pt compounds.

3.4.4. Other Routes

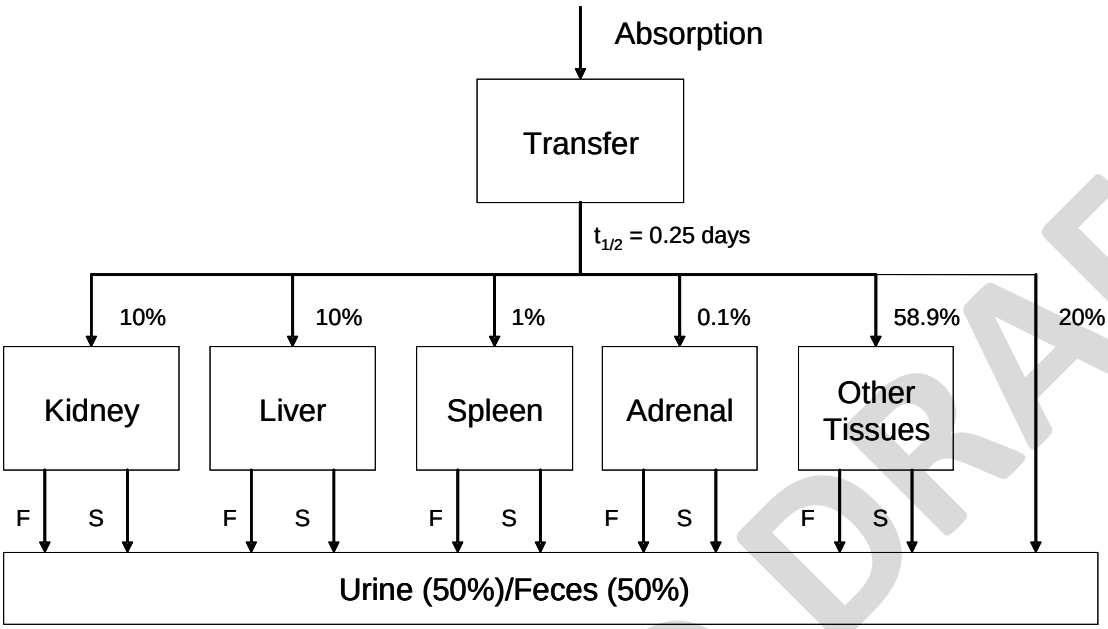
Moore et al. (1975b, c) measured whole-body retention kinetics and urinary and fecal excretion of Pt following a single intravenous administration of a tracer dose of [$^{191,193}PtCl_4$] to male CD-1 rats (n = 20). Whole-body retention for the first 28 days following the dose was measured by whole-body counting of [^{191}Pt] gamma activity; urine and fecal Pt was also measured by counting [^{191}Pt] gamma activity of samples collected in metabolic cages. The pseudo-first-order whole-body elimination half-time was approximately 10 days (estimated from digitization of data presented in Figure 4 of Moore et al., 1975b). Data on urine and fecal ^{191}Pt activity for the first 14 days following the dose were reported; urine:fecal excretion ratios ranged from 1 to 2.5 during this period (estimated from data presented in Figure 6 of Moore et al., 1975b).

Artelt et al. (1999a) measured urinary and fecal excretion of Pt for 10 days following a single intravenous administration of 500 μg Pt as K_2PtCl_4 to female Lewis rats (n = 8). Pt in excreta was measured by ICP-MS (see Section 3.1.1). Approximately 50% of the administered dose was excreted in urine in 10 days and 41% was excreted in feces (these values presumably represent group mean, SD values were not reported).

In summary, the above studies (Artelt et al., 1999a; Moore et al., 1975b, c) provide evidence for fecal excretion of Pt following absorption of K_2PtCl_4 or $PtCl_4$, and provide evidence for urine:fecal excretion ratios of absorbed Pt that range from 1 to 2.5. The nearly comparable rates of urinary and fecal excretion of Pt that were observed following intravenous administration of $PtCl_4$ suggest that the much lower urine:fecal excretion ratios (e.g., <0.1) observed during the first 1–2 days following inhalation exposures to this compound (Moore et al., 1975a) are contributed by mucociliary clearance of Pt deposited in the respiratory tract to the GI tract.

3.5. PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

The International Commission on Radiological Protection (ICRP, 1981) developed a multicompartmental model of the toxicokinetics of Pt in humans (Figure 3-1). This model was developed for the purpose of estimating radiation doses resulting from absorbed radioactive Pt nucleotides and, therefore, simulates the post-absorption distribution and excretion of Pt (i.e., irrespective of the chemical or physical form ingested or inhaled). The model is reportedly based largely on the data reported in Moore et al. (1975a, b) and Yoakum et al. (1975); however, specific connections between parameter values and the latter studies are not discussed in detail in ICRP (1981). Information on calibration and evaluation of the model is not discussed in ICRP (1981) and does not appear available elsewhere.



F = 95%, $t_{1/2}$ = 8 days

S = 5%, $t_{1/2}$ = 200 days

The ICRP (1981) model simulates the kinetics of elimination of absorbed Pt. Absorbed Pt enters a transfer compartment, from which Pt is distributed ($t_{1/2}$ = 0.25 days) to kidney (10%), liver (10%), spleen (1%), adrenals (0.1%), and other tissues (58.9%). Biphasic elimination of Pt from tissues is simulated as fast (F, $t_{1/2}$ = 8 days, 95% of burden) and slow (S, $t_{1/2}$ = 200 days, 5% of burden) first-order excretion in urine and feces, in a 1:1 mass ratio.

Figure 3-1. ICRP (1981) model of Pt toxicokinetics in humans.

The ICRP (1981) model includes several compartments including a central (transfer) compartment that receives absorbed Pt (e.g., from the GI tract or respiratory tract), and other compartments representing the kidney, liver, spleen, adrenals, other tissues, feces, and urine. Each tissue is composed of two subcompartments, representing pools of Pt that are assumed to make faster ($t_{1/2}$ = 8 days) or slower ($t_{1/2}$ = 200 days) contributions to Pt excretion kinetics. Excretion of Pt in feces and urine is represented with direct transfers from each tissue to excreta (urine:feces ratio = 1:1). This approach accounts for the relative contribution made by the Pt burdens in each tissue to excretion, rather than providing a simulation of physiological pathways of excretion (i.e., transfer directly from kidney to urine, transfer from liver to feces, transfer from other tissues to urine via a central compartment). Transfers of Pt from the central compartment to tissues and from tissues to excreta are assumed to follow first-order kinetics. Each transfer is represented with a single rate coefficient (day^{-1}). Age-dependency of transfer or other factors that might affect intercompartment transfer rates (e.g., differences between Pt compounds) are not represented in the model. The total transfer rate from the central compartment to all

destinations combined is assumed to be 2.77 day^{-1} ($t_{1/2}$ = 0.25 day). Values for transfer coefficients from the central compartment to tissues and tissue compartments are based on assumed deposition fractions (DFs) or instantaneous fractional outflows of Pt between compartments, where the transfer coefficient to a specific tissue or compartment (TP_i) is given by:

$$TP_i = DF_i \cdot TPALL \qquad \textbf{Eq. (3-1)}$$

This approach establishes mass balance with respect to the transfer rates from plasma:

$$\sum TP_i = TPALL \qquad \textbf{Eq. (3-2)}$$

DFs and corresponding transfer coefficients calculated from Equation 3-1 for each compartment are presented in Table 3-1.

Table 3-1. Parameters and values in ICRP (1981) Pt biokinetics model

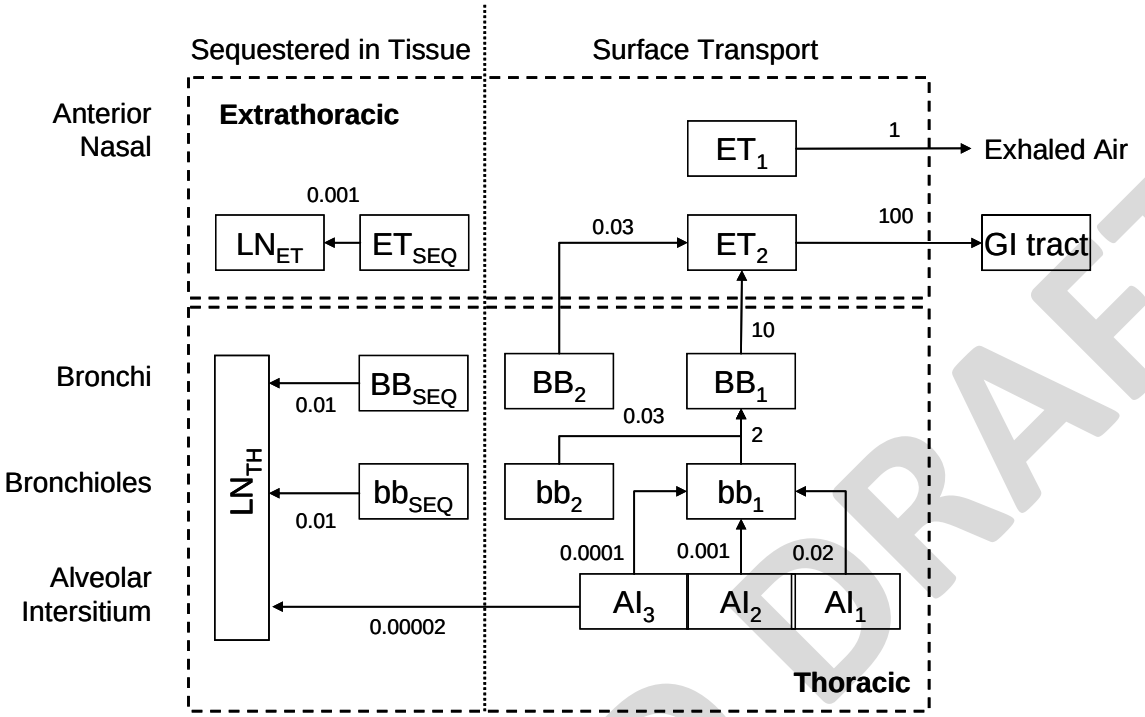
Parameter	DF	Half-time (day)	Rate (day^{-1})	Description
TRTI	1.000	0.25	2.77	Transfer to tissues
TRKI(1)	0.095	0.25	2.63×10^{-1}	Transfer to kidney(1)
TRKI(2)	0.005	0.25	1.39×10^{-2}	Transfer to kidney(2)
TRLI(1)	0.095	0.25	2.63×10^{-1}	Transfer to liver(1)
TRLI(2)	0.005	0.25	1.39×10^{-2}	Transfer to liver(2)
TRSP(1)	0.010	0.25	2.63×10^{-2}	Transfer to spleen(1)
TRSP(2)	0.001	0.25	1.39×10^{-3}	Transfer to spleen(2)
TRAD(1)	0.001	0.25	2.63×10^{-3}	Transfer to adrenal(1)
TRAD(2)	0.000	0.25	1.39×10^{-4}	Transfer to adrenal(2)
TROT(1)	0.560	0.25	1.55	Transfer to other tissue(1)
TROT(2)	0.029	0.25	8.17×10^{-2}	Transfer to other tissue(2)
KI(1)FE	1.000	200	3.47×10^{-3}	Kidney(1) to feces
KI(1)UR	1.000	8	8.66×10^{-2}	Kidney(1) to urine
KI(2)FE	1.000	200	3.47×10^{-3}	Kidney(2) to feces
KI(2)UR	1.000	8	8.66×10^{-2}	Kidney(2) to urine
LI(1)FE	1.000	200	3.47×10^{-3}	Liver(1) to feces
LI(1)UR	1.000	8	8.66×10^{-2}	Liver(1) to urine
LI(2)FE	1.000	200	3.47×10^{-3}	Liver(2) to feces
LI(2)UR	1.000	8	8.66×10^{-2}	Liver(2) to urine
SP(1)FE	1.000	200	3.47×10^{-3}	Spleen(1) to feces
SP(1)UR	1.000	8	8.66×10^{-2}	Spleen(1) to urine
SP(2)FE	1.000	200	3.47×10^{-3}	Spleen(2) to feces
SP(2)UR	1.000	8	8.66×10^{-2}	Spleen(2) to urine
AD(1)FE	1.000	200	3.47×10^{-3}	Adrenal(1) to feces
AD(1)UR	1.000	8	8.66×10^{-2}	Adrenal(1) to urine
AD(2)FE	1.000	200	3.47×10^{-3}	Adrenal(2) to feces
AD(2)UR	1.000	8	8.66×10^{-2}	Adrenal(2) to urine
OT(1)FE	1.000	200	3.47×10^{-3}	Other tissue(1) to feces
OT(1)UR	1.000	8	8.66×10^{-2}	Other tissue(1) to urine
OT(2)FE	1.000	200	3.47×10^{-3}	Other tissue(2) to feces
OT(2)UR	1.000	8	8.66×10^{-2}	Other tissue(2) to urine

Tissue compartments are composed of faster (1) and slower (2) pools for Pt excretion. Rates are first-order constants (day^{-1}) calculated as: rate = $\ln(2)/t_{1/2}$

AD = adrenal; DF = deposition fraction; KI = kidney; FE = feces; LI = liver; SP = spleen; TR = transfer compartment; UR = urine

Although the ICRP (1981) model is intended to simulate the distribution and elimination of absorbed Pt, other ancillary models developed by ICRP can be applied to estimate the absorbed dose inputs to the post-absorption kinetics model. ICRP (1981) assigned a value of 0.01 (i.e., 1%) for the GI absorption fraction of all Pt compounds and based this assignment on the Moore et al. (1979b, c) study of relatively soluble $PtCl_4$. ICRP (1994) developed a generic model for simulating lung deposition and clearance of inhaled particulates in humans. The model can be implemented to simulate deposition, retention, and absorption of inhaled Pt, when

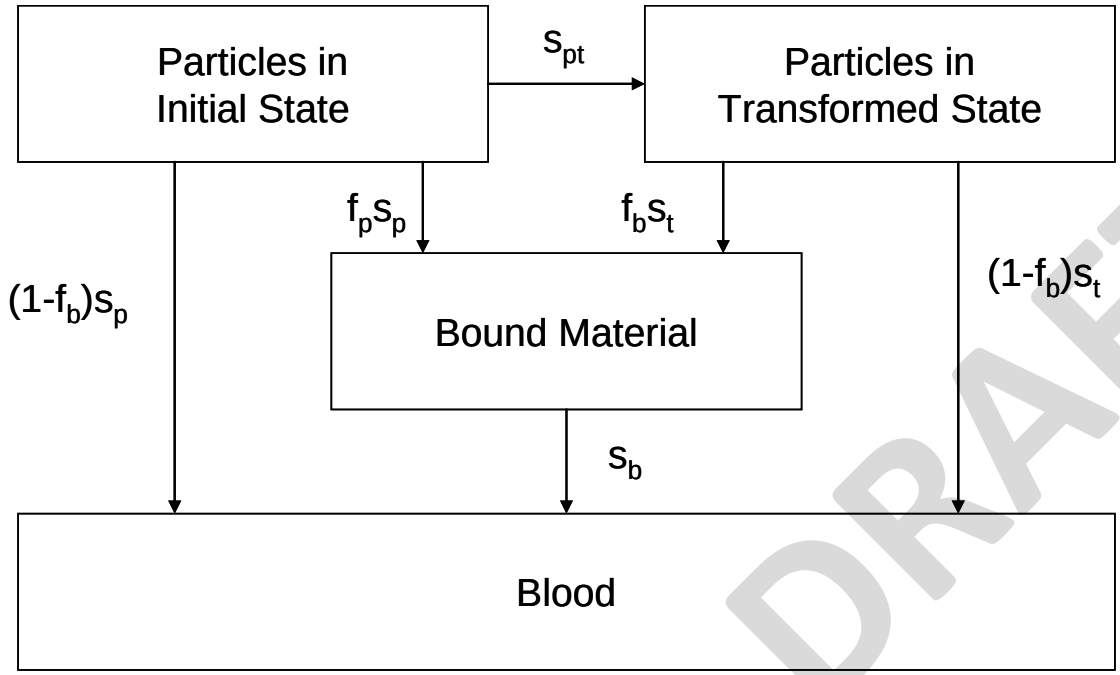
specific parameters values for inhaled particle size and Pt absorption are used in the model. The general form of the model represents the respiratory tract as a series of compartments representing the extrathoracic, bronchial, bronchiolar, and alveolar-interstitium regions of the tract (Figure 3-2). Each compartment is assigned age- and particle-size-dependent DFs (i.e., fraction of inhaled particles deposited in each compartment). Nose- and mouth-breathing pathways are simulated, which vary in relative contribution, depending on age and activity level. Within each compartment, particulates can be deposited, sequestered into tissue, transported to other compartments (i.e., mechanical clearance), or dissolved and absorbed (Figure 3-3). Transport between compartments is assumed to follow first-order kinetics and, for Pt, are independent of the chemical or physical form of the Pt compound that is inhaled. Dissolution and absorption parameters in the model are chemical specific; absorption parameters for Pt are presented in Table 3-2. ICRP (1981) assigned all Pt compounds to the fast absorption category, in which dissolution rate is assumed to be 100 day^{-1} ($t_{1/2} \approx 10$ minutes). The basis for this categorization is reported in ICRP (1981) as the observation reported in Moore et al. (1975a) that "platinum whether inhaled as the metal, the oxide or the sulfate is rapidly translocated from the lungs". This categorization reflects a revision in the ICRP (1981) report from a previous categorization in which Pt compounds were classified into clearance categories as follows: oxides and hydroxides, Y (pulmonary absorption $t_{1/2}$ = 365 days); halides and nitrates, W (pulmonary absorption $t_{1/2}$ = 90 days); and all other, D (pulmonary absorption $t_{1/2}$ = 30 minutes).



AI = alveolar-interstitial; BB = bronchial; bb = bronchiolar; ET = extrathoracic; LN = lymph nodes; SEQ = sequestered; TH = thoracic

The ICRP (1994) model simulates surface transport (e.g., mucocilliary) and sequestration into tissues. Numbers are default values for first order rate constants (day^{-1}) and represent combined rates of transport by all contributing mechanisms (e.g., mucocilliary, macrophages) in each compartment.

Figure 3-2. Generic ICRP (1994) model of transport of particles deposited in regions of the respiratory tract.



The generic ICRP (1994) model of absorption includes: dissolution (s); transformation, in which the particle in the initial state, with dissolution rate s_p, is transformed at rate s_{pt} to a form having a dissolution rate s_t; and binding, which results in absorption rate, s_b; unbound dissolved materials are absorbed instantaneously. Each process acts, at the same rates, on all compartments in each region of the respiratory tract except ET_1 (see Figure 3-2), where no absorption occurs. Absorption parameter values are grouped into classes (fast, moderate, slow), to which specific chemical compounds are assigned (see Table 3-2). Particle transport rates are the same for particles in the initial and transformed states; however, bound material is not subject to particle transport.

Figure 3-3. Generic ICRP (1994) model of absorption of particles deposited in the respiratory tract.

Table 3-2. Default parameter values for ICRP (1994) model of absorption of inhaled particulates

Parameter	Absorption behavior class		
	F (fast)	M (moderate)	S (slow)
Initial dissolution rate (d^{-1}), s_p	100	10	0.1
Transformation rate (d^{-1}), s_{pt}	0	90	100
Transformed dissolution rate (d^{-1}), s_t	–	0.005	0.0001
Fraction to bound state, f_b	0	0	0
Absorption rate from bound state (d^{-1}), s_b	–	–	–

Initial dissolution half-times range from approximately 10 minutes (F) to 7 days (S). Transformed dissolution half-times range from approximately 140 days (M) to 19.5 years (S). Prior to ICRP (1981), Pt compounds were classified as follows: oxides and hydroxides, Y (pulmonary absorption $t_{1/2}$ = 365 days, k ≈ 0.00190 day^{-1}); halides and nitrates, W (pulmonary absorption $t_{1/2}$ = 90 days, k ≈ 0.00770 day^{-1}); and all other, D (pulmonary absorption $t_{1/2}$ = 30 minutes, K ≈ 33.3 day^{-1}).

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

4.1.1. Oral

A single case study reports effects of intentional ingestion of a photographic solution containing 600 mg of potassium chloroplatinite (a synonym for the halogenated Pt salt potassium tetrachloroplatinate K_2PtCl_4) by a 31-year-old man (Woolf and Ebert, 1991). Toxic effects included acute oliguric renal failure, metabolic acidosis, fever, muscle cramps, gastroenteritis, and rhabdomyolysis. Abnormal laboratory finding included elevated liver enzymes and blood neutrophil and eosinophil counts. All signs and symptoms of toxicity resolved within 6 days with supportive medical management. No additional reports of oral exposure of humans to Pt or Pt compounds were identified.

4.1.2. Inhalation

Pt-group metals are refined through a series of solubilization and precipitation processes involving acids (usually hydrochloric acid) to obtain purified halogenated metal salts, and, with further processes, the elemental metals. Refinery workers are expected to be exposed to various types of PGE salts and metals, and other airborne non-PGE respiratory irritants, depending on their job responsibilities (Merget et al., 2000; Maynard et al., 1997; Biagini et al., 1985a). Numerous case studies and epidemiological studies of occupational exposure to halogenated Pt salts and Pt compounds are available. Studies can be generally categorized based on Pt compound class (e.g., soluble or insoluble); however, for most occupational exposures, it is unlikely that workers are exposed to a single Pt compound or class of Pt compounds.

Occupational exposures to Pt compounds in refineries and catalyst production plants are to a mixture of soluble Pt compounds (mainly halogenated Pt salts in the form of chloroplatinates) and insoluble Pt compounds (principally Pt metal, PtO, and PtO_2) (Merget et al., 1999). Exposure measurements of Pt concentrations in occupational studies are generally reported as total Pt or soluble Pt. As discussed in detail in Chapter 2, total Pt (i.e., Pt in all chemical forms and oxidation states present in the sample) is measured following complete sample digestion with quantitative determination often using ICP-MS (Barefoot and Van Loon, 1999). Determination of soluble Pt requires the additional step of sample extraction into a solution (e.g., water, dilute hydrochloric acid, or nitric acid). The soluble fraction is an operationally-defined fraction of Pt in which many different species of Pt can be present depending on the extraction solution. As such, characterization of Pt from occupational or environmental samples as "soluble Pt" does not provide information regarding the chemical species present in a sample. When samples contain halogenated Pt salts, these compounds are

likely to be a portion of the soluble Pt reported because of their solubility in water and other common extraction solutions (see Table 2-1). In this document, the term soluble Pt compounds primarily includes $Pt(SO_4)_2$, tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$), and the halogenated Pt salts. However, no occupational studies were identified that report speciation of Pt compounds, analytical characterization of Pt compounds, specific measurements of halogenated Pt compounds, or estimations of the fraction of soluble Pt represented by halogenated Pt compounds.

Most case reports and older studies reporting health effects associated with Pt exposure attribute health effects to halogenated Pt salts based on processes utilized in the refining of Pt; however, these studies do not report exposure data (e.g., Jarabek et al., 1984; Dally et al., 1980; Milne et al., 1970; Parrot et al., 1969; Roberts, 1951). The work environment of a Pt refinery or Pt catalyst production plant where individuals become sensitized to Pt compounds involves exposure to halogenated Pt salts, mainly chloroplatinates (e.g., ammonium hexachloroplatinate, sodium hexachloroplatinate, potassium hexachloroplatinate, and chloroplatinic acid), because these compounds are required for the processes involved (Merget, 2000; Merget et al., 1999; Parrot et al., 1969; Hunter et al., 1945). For example, inhalation exposure to Pt compounds in a Pt refinery includes exposure to the complex halogenated Pt salt ammonium hexachloroplatinate ($[NH_4]_2PtCl_6$) or sodium hexachloroplatinate ($NaPtCl_6$) because Pt is precipitated in the form of one of these complex halogenated salts in whatever method is used in refining (Parrot et al., 1969; Hunter et al., 1945).

Even in occupational studies that contain some exposure measurements, data are generally restricted to semi-quantitative measures such as percent of measurements where air concentrations exceeded 2 μg soluble Pt/m^3 (e.g., Calverley et al., 1995). Five epidemiological studies report both health effects and Pt exposure measurements including data on total and soluble Pt (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990). No occupational studies were identified that report speciation of Pt compounds, analytical characterization of Pt compounds, or specific measurements of halogenated Pt compounds. Although inhalation is considered to be the predominant route for occupational exposure, the potential for a dermal exposure component cannot be ruled out. Workplace atmospheres in precious metal refineries in the United States (Baker et al., 1990) and South Africa (Calverley et al., 1995) frequently exceeded the Occupational Safety and Health Administration (OSHA) occupational limit for Pt salts of 2 μg soluble Pt/m^3, but lower exposures to Pt salts are expected in modern PGE catalyst production plants due to more uniform production processes and implemented protective measures (Merget et al., 2000).

Health and toxic effects in humans repeatedly exposed to Pt metal or Pt compounds by inhalation are documented in numerous case reports and epidemiologic studies and include respiratory irritation and effects associated with allergic sensitization. Other adverse health

effects (e.g., those effects not related to respiratory irritation or allergic sensitization) have not been reported.

Individuals with halogenated Pt-salt allergic sensitization showed progression to moderate or severe asthma with continued exposure (Merget et al., 1999). For halogenated Pt salts and other sensitizers, effects of work-related allergic sensitization may be severe and disabling (Friedman-Jimenez et al., 2000). Severe cases of allergic sensitization to halogenated Pt salts included workers with bluish skin due to insufficient oxygen in blood, feeble pulse, and extreme difficulty breathing, which required the subject to remain upright to breathe (Roberts, 1951). The effects and time-course of allergic sensitization to halogenated Pt salts are consistent with an IgE-mediated, Type I response (see Section 4.6.3.1, *Sensitization* for additional details). Data on the health effects of chronic Pt exposure in workers following the development of Pt allergic sensitization are complicated by the practice of medically terminating or transferring workers to areas with lower Pt exposure (e.g., Merget et al., 2001, 2000; Calverley et al., 1995; Brooks et al., 1990). Although no deaths were reported for Pt-specific allergic sensitization, two cases of occupational asthma leading to death have been reported after medical recommendations to permanently cease exposure to other low molecular weight sensitizers (isocyanates) had been given but not followed (Friedman-Jimenez et al., 2000). Even following the work practice of medical termination, about 50% of workers with allergic sensitization to halogenated Pt salts continue to experience symptoms such as asthma and shortness of breath on exertion several years after removal from exposure (Merget et al., 1999, 1994).

Signs and symptoms consistent with respiratory irritation and allergic sensitization have been observed in workers exposed to Pt in several types of work environments, including photographic studios using halogenated Pt salts (Hunter et al., 1945); jobs applying halogenated Pt salts by brush to anodes (Harris, 1975); refinement of Pt involving halogenated Pt salts (Raulf-Heimsoth et al., 2000; Santucci et al., 2000; Linnett and Hughes, 1999; Newman Taylor et al., 1999; Calverley et al., 1999, 1995; Merget et al., 1999, 1996, 1994, 1991, 1988; Niezborala and Garnier, 1996; Bolm-Audorff et al., 1992; Brooks et al., 1990; Baker et al., 1990; Venables et al., 1989; Biagini et al., 1985a; Jarabek et al., 1984; Hughes, 1980; Dally et al., 1980; Cromwell et al., 1979; Cleare et al., 1976; Milne, 1970; Parrot et al., 1969; Roberts, 1951; Hunter et al., 1945); and exposure to halogenated Pt salts in the production of Pt catalysts (Cristaudo et al., 2005; Merget et al., 2002, 2001, 2000, 1999, 1996, 1995; Raulf-Heimsoth et al., 2000).

Numerous epidemiology and case studies report that inhalation exposure to Pt compounds, specifically halogenated Pt salts, is associated with the development of allergic sensitization; other toxic effects associated with inhalation exposure of humans to Pt compounds have not been reported (review and detailed discussion of available evidence is provided below in Section 4.1.2.1, *Soluble Pt Forms*). In contrast to the numerous publications on exposure to soluble Pt compounds, very little information is available on health effects of insoluble Pt compounds (details are discussed in Section 4.1.2.2, *Insoluble Pt Forms*). However, the

available evidence from studies of inhalation of insoluble Pt compounds has not demonstrated effects.

4.1.2.1. Soluble Pt Forms

As discussed above, many case reports and epidemiology studies provide evidence that workers exposed to halogenated Pt salts develop allergic sensitization to Pt compounds. Information to characterize the exposure-response relationship for the development of halogenated Pt salt sensitivity is available from five epidemiological studies (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990); details of these five studies are provided in Section 4.1.2.1.2 (*Toxicity of soluble forms of Pt: epidemiological evidence of Pt allergic sensitization*). Although exposure is generally not characterized in the available occupational studies beyond soluble Pt, there is some evidence that halogenated Pt salts may have different sensitizing potencies. The toxicity and solubility of halogenated Pt salts (compounds generally considered soluble in the literature) appear to be related to the halogen-ligands coordinated to Pt and the negative charge of these complexes (Nischwitz et al., 2004; Ravindra et al., 2004; Rosner and Merget, 2000; Cleare et al., 1976). In particular, results of the retrospective study by Linnett and Hughes (1999) suggest that chloroplatinate salts are allergenic, as are chloroplatinates in combination with tetraamine Pt dichloride, but tetraamine Pt dichloride does not show any strong evidence of being a sensitizer. A high incidence of allergic sensitization to halogenated Pt salts was observed among refinery workers exposed to chloroplatinates (106 of 270 workers) or to chloroplatinates with co-exposure to tetraamine Pt dichloride (5 of 31 workers), but no cases were observed among 39 workers exposed to tetraamine Pt dichloride alone in the production of automotive catalysts (study details provided in Section 4.1.2.1.2, *Toxicity of soluble forms of Pt: epidemiological evidence of Pt allergic sensitization*). Similar results were reported by Steinfort et al. (2008) in a prospective study of workers at a catalyst manufacture plant in Melbourne, Australia, where no cases of positive skin prick test (SPT) were noted among workers with reported exposure to tetraamine Pt dichloride. The authors report that tetraamine Pt dichloride, palladium, and rhodium were utilized in the plant, but do not report any speciation data to identify specific Pt compounds. Steinfort et al. (2008) report three air measurements of between 10 and 20 g/m^3, but do not list methods used to measure Pt, whether the reported concentrations were total or soluble, or limits of detection. Of the 112 total workers, the authors reported that 71 had exposure to tetraamine Pt dichloride, 41 were in the high-exposure areas, and 26 of the high-exposure workers had at least two examinations. None of the 26 workers had a positive SPT or symptoms of allergic sensitization to Pt based on forced expiratory volume in 1 second (FEV_1) or general respiratory symptoms. Although the authors report that exposure was to tetraamine Pt dichloride, the SPT was performed with hexachloroplatinic acid (1.471 g/kg).

Supportive evidence for the allergenic activity of halogenated Pt salts also is provided by dermal and parenteral studies conducted in animals (Dearman et al., 1998; Schuppe et al., 1997a, b, 1992); evidence for airway effects of inhaled halogenated Pt salts (specifically to salts of hexachloroplatinate) is provided by studies in monkeys (Biagini et al., 1986, 1985b, 1983). Parenteral studies in animals also provide evidence supporting the findings of Linnett and Hughes (1999) and Steinfort et al. (2008) that tetraamine Pt dichloride may not have sensitization properties (Schuppe et al., 1997b). Details of animal studies are provided in Section 4.5.1.1, *Sensitization Studies, Soluble Pt Salts*.

Additional supportive evidence on the variable allergenic potency of soluble Pt compounds comes from a study by Cleare et al. (1976) on 18 refinery workers with known Pt sensitivity and on the characterization portion of a study of 22 catalyst production plant workers with Pt sensitivity in Cristaudo et al. (2005). In the Cleare et al. (1976) study, SPTs (defined in detail in Section 4.1.2.1.1 below) were performed on workers using 21 different Pt compounds (including some isomers); however, not all compounds were tested in all workers. No information on the study population, other than that workers were employed in a Pt refinery and were known to be sensitive to halogenated Pt salts (specifically to salts of hexachloroplatinate), was reported. For each compound tested, the initial SPT was conducted by injecting a volume of approximately 3×10^{-6} mL of a solution containing 10^{-9} g/mL of the specific compound (e.g., a dose of approximately 10^{-15} g). If no reaction was observed within 10 minutes, a 10-fold higher concentration was used; this step-wise process was continued until a positive response was observed or the maximum test solution concentration of 10^{-3} g/mL was reached. Ammonium hexachloroplatinate [$(NH_4)_2$ $PtCl_6$] was used as the positive control. Results were presented for individual workers. Two workers did not show a positive reaction to ammonium hexachloroplatinate and were used as negative controls; these workers also did not show a positive SPT to other Pt compounds tested. Results of the SPT in the remaining 16 workers suggest that the degree of allergic reaction was related to the number of chlorine atoms in a series of halogenated Pt salts. Sensitivity showed the following order of decreasing allergenicity: $(NH_4)_2[PtCl_6] \approx (NH_4)_2[PtCl_4] > Cs_2[Pt(NO_2)Cl_3] > Cs_2[Pt(NO_2)_2Cl_2] > Cs_2[Pt(NO_2)_3Cl] > K_2[Pt(NO_2)_4]$ (inactive). Other nonallergenic Pt compounds in this study included *cis*-$[Pt(NH_3)_2Cl_2]$; *trans*-$[Pt(NH_3)_2Cl_2]$; *cis*-$[Pt(CH_3NH_3)_2Cl_2]$; *trans*-$[Pt(CH_3NH_3)_2Cl_2]$; *trans*-$[Pt(CH_2OHNH_2)_2Cl_2$; *cis*-$(Pt(NH_3)_2(H_2O_2)_2(NO_3)_2$; and $[Pt(NH_3)_4]Cl_2$. Exchanging bromine for chlorine appeared to reduce the allergenicity, with a similar distribution of potency as for the chlorine-containing compounds.

In a study of 153 workers in a catalyst production plant reported by Cristaudo et al. (2005), workers were subject to a medical questionnaire, SPT to common aeroallergens, SPT to chloride salts of Pt ($H_2[PtCl_6]$, $K_2[PtCl_4]$, $Na_2[PtCl_6]$) and other PGEs ($IrCl_3$, $RhCl_3$, $PdCl_2$), and patch tests to $H_2[PtCl_6]$ and $PdCl_2$. The SPTs to common allergens were performed with 16 common diagnostic inhalants including dusts, pollens, molds, animals, and controls. No

exposure data were reported; however, the authors separated workers into three categories based on exposure potential (high—workers on the production and refining side of the plant; low—workers in all other production areas; and no—office workers outside the production area). Positive SPTs were reported for 22 of the 153 workers to one or more of the PGEs at various concentrations. None of the 11 office workers had a positive SPT, while 14/105 or 13.3% of workers in the low-exposure group had a positive SPT to halogenated Pt salts and 9/37 or 24.3% of workers in the high-exposure group had a positive SPT to halogenated Pt salts. All of the workers with a positive SPT were positive to hexachloroplatinic acid ($H_2[PtCl_6]$) and the authors suggest that their data support the use of hexachloroplatinic acid as the most important Pt salt to test for allergy to halogenated Pt salts. A subset of the 22 workers positive to hexachloroplatinic acid were positive to all other PGE salts tested except for palladium, which was negative in all SPTs and only positive in one individual by patch test. Positive results for SPT to $H_2[PtCl_6]$, $K_2[PtCl_4]$, $Na_2[PtCl_6]$, $IrCl_3$, $RhCl_3$, are as follows: seven workers were positive to $H_2[PtCl_6]$ only, eight workers were positive to all halogenated Pt salts tested, three workers were positive to $H_2[PtCl_6]$ and $Na_2[PtCl_6]$, four workers were positive to $H_2[PtCl_6]$ and $K_2[PtCl_4]$, two workers were positive to all five PGEs, and one individual was positive to all but $RhCl_3$.

Forty workers had positive SPTs to the common allergens and Cristaudo et al. (2005) used this information to separate the workers into four groups based on response to allergological tests (negative, positive to common allergens, positive to halogenated Pt salts, and positive to both common allergens and halogenated Pt salts). Symptoms of eczema did not differ substantially between groups (6–13% prevalence). Symptoms of rhinitis were low in workers classified as negative (5.1%) and high in all allergic groups (90.6, 73.3, and 87.5% in workers positive to common allergens, halogenated Pt salts, and both common allergens and halogenated Pt salts, respectively). The prevalence of asthma and urticaria was higher in workers with halogenated Pt salt allergy only (asthma—46.7%; urticaria—26.7%) and workers with halogenated Pt salt allergy and positive response to common allergens (asthma—37.5%; urticaria—25.0%). The authors analyzed age, atopy, smoking, and years at work by univariate and multivariate analyses to assess these variables as potential risk factors for predicting positive SPT to halogenated Pt salts. They did not detect any effect of age, but found a slight increase in prevalence for atopy (adjusted odds ratio = 2.2, 95% CI = 0.8–6.0). The prevalence of positive SPTs to halogenated Pt salts was almost equal between smokers and nonsmokers (adjusted odds ratio = 1.1, 95% CI = 0.4–3.0). The workers were separated into two categories based on years on the job (0–5 and 6–30 years). Workers with ≥6 years of work had an increased risk of developing a positive SPT to halogenated Pt salts (adjusted odds ratio = 3.2, 95% CI = 1.2–8.9).

Cleare et al. (1976) noted that most of the nonallergenic Pt compounds were neutral (nonionic) compounds, with the exception of $K_2[Pt(NO_2)_4]$. Cleare et al. (1976) proposed that Pt complexes with strongly bound ligands (e.g., $K_2[Pt(NO_2)_4]$; *cis*-$[Pt(NH_3)_2Cl_2]$) having poor leaving abilities (e.g., NO_2, NH_3, which are not easily displaced by a nucleophile) are not

allergenic, presumably due to little or no reaction with proteins. As discussed in Section 4.6.3.1 (*Mode of Action, Sensitization*), allergenic Pt compounds are expected to be haptens, compounds that elicit an allergenic response only when attached to a large carrier molecule (typically, a protein) (Rosner and Merget, 1990). Findings by Linnett and Hughes (1999) on the occurrence of allergic disease in workers exposed to chloroplatinates, but not in workers exposed to tetraamine Pt dichloride, support the results of Cleare et al. (1976) showing that allergenic potential may be related to the degree of chlorination. However, the Linnett and Hughes (1999) study does not include exposure data on the particular Pt compounds to which workers are exposed; workers were instead classified by work area without speciated Pt exposure data. Results of studies in animals provide supportive data on the relationship of allergenic potential and the degree of chlorination (Murdoch and Pepys, 1986, 1985, 1984a, b; Schuppe et al., 1997a, 1992); study details are provided in Section 4.5.1.1 (*Sensitization Studies, Soluble Pt Salts*). Together, results of these studies suggest that highly chlorinated forms of halogenated Pt salts (such as hexachloroplatinate and tetrachloroplatinate salts) may have a relatively higher potential to induce sensitization than less-chlorinated forms. However, results of the Cleare et al. (1976) study also indicate that halogenated Pt salts with other halogens as ligands (e.g., bromine) may also have allergenic activity.

In summary, an association between exposure of workers to halogenated Pt salts and the development of allergic sensitization is indicated by numerous case reports and epidemiology studies. The available studies suggest that halogenated Pt salts induce allergic sensitization resulting in asthma, rhinitis, conjunctivitis, and dermatitis. However, all soluble Pt compounds may not have allergenic activity. Evidence from the retrospective epidemiology study by Linnett and Hughes (1999) and from the SPT study by Cleare et al. (1976) and Cristaudo et al. (2005) suggest that the allergenic activity of halogenated Pt salts may differ among the compounds. Supporting evidence for compound-specific allergenic activity is also available from studies in animals (see Section 4.5.1.1).

4.1.2.1.1. ***Toxicity of soluble forms of Pt: diagnosis of Pt allergic sensitization.*** Most cases of allergic sensitivity to Pt are thought to be due to Type I, immediate onset, IgE-mediated immune mechanisms to halogenated Pt salts (Murdoch and Pepys, 1987; Murdoch et al., 1986; Biagini et al., 1986; Hughes, 1980; Cromwell et al., 1979; Pepys et al., 1979). Briefly, IgE-mediated Type I hypersensitivity reactions involve IgE-mediated release of histamine and other mediators from degranulation of mast cells and basophils. The reaction is classified as "immediate", because the mediators released by degranulation act quickly to produce effects. Initial exposure to an allergen (also known as "sensitizing exposure") is required for IgE antibodies to be produced and sensitization effects to occur on subsequent exposures (although not necessarily the next exposure). As discussed in Section 4.6.3.1 (*Mode of Action Information, Sensitization*), the clinical presentation of halogenated Pt salt sensitization is consistent with an IgE-mediated

reaction (see Section 4.6.3.1 for additional details on Type I hypersensitivity reactions). However, evidence suggests that non-IgE mechanisms may also be involved in some of the hypersensitivity responses to halogenated Pt salts. Results of a study on the passive transfer (via serum) of halogenated Pt salt-allergy to non-exposed humans and monkeys suggest that an additional IgG-mediated mechanism may be involved in the development of halogenated Pt salt allergy (Pepys et al., 1979; study details are summarized in Section 4.5.1.1.2). IgG-mediated hypersensitivity reactions are classified as Type II or Type III. Unlike IgE-mediated hypersensitivity reactions, Type II- and Type III-mediated reactions do not involve an immediate degranulation of mast cells and basophils. Details of IgG-mediated mechanisms of hypersensitivity are discussed in Section 4.6.3.1. In addition, evidence that halogenated Pt salts (specifically to salts of hexachloroplatinate) can produce respiratory effects in the absence of IgE-mediated sensitization was reported in a study in monkeys by Biagini et al. (1985b) (see Section 4.4.2 for study details).

The diagnosis of sensitization to halogenated Pt salts, as reviewed by Merget (2000), is based on the occurrence of respiratory or dermal symptoms in the work place, documentation of disease status (asthma, rhinitis, conjunctivitis, urticaria), and a positive SPT (discussed in detail below) with a hexachloroplatinate salt. Asthma is usually documented with tests of lung function (e.g., FEV_1, forced expiratory flow [FEF], peak expiratory flow [PEF]), or bronchial responsiveness to nonspecific stimuli (e.g., methacholine, histamine, or cold air) or specific stimuli (e.g., in this case, halogenated Pt salts). The pathogenesis of bronchial hyperresponsiveness and asthma involves several mechanisms, including inflammation, enhanced neuromuscular responses, and allergic reactions (Barnes, 1989); thus, although bronchial hyperresponsiveness may be mediated through a Type I hypersensitivity reaction, bronchial hyperresponsiveness also may occur in the absence of an IgE-mediated response (see Sections 4.6.3 for additional details). To definitively demonstrate bronchial hyperresponsiveness to a halogenated Pt salt, a bronchial challenge test must be performed using that specific stimulus. The specific stimulus test examines the effect of inhalation (typically 10 breaths) of nebulized solutions containing that substance on baseline pulmonary function test results. A positive response to an allergen is typically defined as a 15–20% decrease in FEV_1 from baseline (Melillo et al., 1991). Although bronchial responsiveness testing using a specific stimulus provides evidence of bronchial reactivity (but not the mechanism producing the effect) to that specific agent, a severe reaction may occur; therefore, bronchial challenge tests are often conducted using nonspecific stimuli to decrease medical risks. The nonspecific stimulus test involves inhalation of increasing doses of a nonspecific challenge agent (most commonly methacholine). Pulmonary function tests are conducted after each dose, until reaching a dose that produces a 15–20% drop in FEV_1 from baseline (called the provocative dose or PD_{15} or PD_{20}); the response to a nonspecific stimulus is quantified by the PD. Nonspecific stimuli do not produce bronchial responsiveness through an IgE-mediated mechanism.

SPTs are routinely performed to diagnose sensitivity to specific halogenated Pt salts (Merget, 2000). Unlike bronchial responsiveness, which involves several mechanisms and may occur in the absence of an IgE-mediated mechanism, SPTs only detect Type I, IgE-mediated sensitization. SPTs are conducted by applying a small amount of the test substance to the skin; the skin is then pricked, introducing the test substance into the epidermis. If IgE-antibodies to a specific allergen are present, the allergen will induce degranulation of mast cells and basophils, resulting in the local release of histamine and other mediators. The response, which typically occurs within 10–15 minutes, is observed as a raised, blanched center surrounded by an area of erythema (e.g., a wheal and flare). The criterion for a positive response typically is a wheal with a diameter of at least 3 or 4 mm (Merget, 2000). Since most cases of allergic sensitivity to Pt are thought to be due to IgE-mediated immune mechanisms (see Section 4.6.3.1, *Mode of Action Information, Sensitization*), sensitivity to specific Pt compounds can be detected through SPTs. However, as discussed above and in Section 4.6.3.1, a non-IgE mechanism of sensitivity to halogenated Pt salts cannot be ruled out. Thus, if sensitivity to halogenated Pt salts is predominantly mediated in an individual through a non-IgE mechanism (e.g., possibly an IgG mechanism), sensitivity would not be detected using the SPT.

As reviewed by Merget and Rosner (1990), demonstration of sensitization by SPT to halogenated Pt salts has a high specificity, and in subjects with positive responses to unspecified bronchial challenges and ongoing exposure, SPTs to halogenated Pt salts have a high sensitivity. For example, among the 13 cases of workers who developed a positive SPT to Pt in a 5-year prospective study of 115 high-exposure catalyst production workers, all displayed symptoms (rhinitis, asthma, or dermatitis), although the symptoms were not work-related in a few of these cases (Merget et al., 2000; study details provided in Section 4.1.2.1.2). An additional six subjects in this group developed work-related symptoms, but did not display positive SPT results (Merget et al., 2000). In a retrospective study of 406 U.K. refinery workers exposed to chloroplatinates, 110 cases of halogenated Pt salt allergy were identified; of these, 100 were SPT positive to Pt (Linnett and Hughes, 1999). Among the 10 Pt SPT negative cases, 1 was positive in a patch test, 1 was positive in a "specific" bronchial challenge test (the study report did not identify challenge agent used, although "specific" implies a chloroplatinate salt), 1 had work-related upper respiratory symptoms, and 7 had bronchospasms at work.

Merget et al. (1991) further explored the relationship between SPT to hexachloroplatinate and bronchial challenge tests with specific (hexachloroplatinate) and nonspecific (methacholine) stimuli in Pt refinery workers. A total of 35 workers from two Pt refineries were initially referred to a pulmonary clinic due to work-related symptoms of Pt sensitization (asthma, conjunctivitis, rhinitis); of these, 27 agreed to participate in Pt SPT and Pt specific and nonspecific bronchial challenge tests. Tests were performed an average 15 months (range 0–132 months) after the workers had been removed from the refining area (reasons for removal were not provided in the report), although 19 workers reported that they still had "occasional"

contact with Pt salts. Test results, however, were not reported based on current or previous exposure, and no quantitative information on exposure was reported. Results of testing showed that 16/27 workers tested positive for all three tests (Pt SPT, Pt bronchial challenge, and methacholine bronchial challenge). Test results of the remaining 11 workers were as follows: 2 workers tested positive to Pt and methacholine bronchial challenge, but negative to Pt SPT; 4 workers tested positive to Pt bronchial challenge, but negative to methacholine bronchial challenge and Pt SPT; 1 worker tested positive to Pt SPT (weak response) and methacholine bronchial challenge, but negative to Pt bronchial challenge; 3 workers tested positive to methacholine positive challenge, but negative to Pt bronchial challenge and Pt SPT; and 1 worker tested negative in all three tests. A positive correlation was observed between the response to the Pt SPT and Pt bronchial challenge test ($r = 0.66$; $p < 0.0008$; $n = 27$), but no correlation was observed between the response to Pt SPT and methacholine bronchial challenge ($r = 0.05$; *p*-value reported as not significant; $n = 27$). Results of this study show that the Pt SPT response does not always predict the respiratory response to inhaled hexachloroplatinate.

After removal from exposure, SPT sensitivity to hexachloroplatinate and asthmatic bronchial responses to halogenated Pt salt and methacholine challenges persist in most workers over a 2-year period. Merget et al. (1994) examined the effect of removal from exposure on Pt SPT sensitivity and bronchial challenge tests in 24 Pt refinery workers who had experienced work-related asthma symptoms. Quantitative data on exposure were not reported. Workers were examined on two occasions; SPT to hexachloroplatinate and bronchial challenge tests to hexachloroplatinate and methacholine were conducted at both examinations. At the initial assessment, 11 workers had current exposure to Pt salts and 13 workers had been removed from exposure for an average of 24 months (range 1–61 months). All 24 workers tested positive in the hexachloroplatinate bronchial challenge test and 23 workers tested positive in the methacholine bronchial challenge test; results of the SPT to hexachloroplatinate conducted at the initial assessment visit were not reported. The average time between the first and second assessments was 20 months (range 8–100). At the second assessment, 17 of the 24 workers reported that they still experienced symptoms of asthma. SPT to hexachloroplatinate converted from positive to negative in three workers and from negative to positive in one worker. The response to bronchial challenge with hexachloroplatinate and methacholine did not change from the initial assessment. The three workers converting from positive to negative in the hexachloroplatinate SPT had positive responses to bronchial challenges tests with hexachloroplatinate and methacholine at the second assessment.

Other responses to halogenated Pt salts include elevations in nonspecific histamine release, Pt-specific IgE levels, and total IgE levels in Pt SPT-positive compared with Pt SPT-negative subjects (Merget et al., 1988; Biagini et al., 1985a; Cromwell et al., 1979). Histamine release and Pt-specific IgE levels are not thought to be useful in diagnosing individual cases of halogenated Pt salt allergy, because the nonspecific high binding affinity of

hexachloroplatinate to IgE antibodies is a confounding factor in using Pt-specific IgE to identify halogenated Pt salt allergy (Merget, 2000). The role of total IgE in halogenated Pt salt allergy is also unclear. It may represent a risk factor (i.e., individuals with elevated total IgE may be more likely to become SPT positive). Alternatively, total IgE may be associated with exposure as reported by Merget et al. (2000, 1999), because ongoing Pt exposure causes an increase in total IgE (Merget et al., 1999). However, total serum IgE can be influenced under several conditions, including atopy (e.g., individuals with a hereditary disposition to develop Type I hypersensitivity to common environmental allergens), seasonal variations in pollens, and exposure (variable or continuous) to other non-Pt allergens (such as animal dander) (Goldsby et al., 2003a). Thus, since total serum IgE can be influenced by many factors and may vary over time in response to those factors, use of total serum IgE to diagnose Pt allergy is limited. Nevertheless, multivariate regression analysis in a 5-year prospective study of halogenated Pt salt allergy in catalyst production workers showed that both exposure category ($p = 0.011$) and elevated total IgE levels ($p = 0.036$) were statistically significant explanatory variables for conversion from a negative to a positive hexachloroplatinate SPT (Merget et al., 2000).

In summary, most cases of allergic sensitivity to Pt are thought to be due to Type I, immediate onset, IgE-mediated immune mechanisms to halogenated Pt salts, although other mechanisms, such as an IgG-mediated mechanism, cannot be ruled out. The diagnosis of sensitization to halogenated Pt salts is based on the occurrence of respiratory or dermal symptoms in the work place, documentation of disease status (asthma, rhinitis, conjunctivitis, urticaria), and a positive SPT with various halogenated Pt salts. Asthma is usually documented with pulmonary function tests, or bronchial responsiveness to nonspecific stimuli (e.g., methacholine) or specific stimuli (e.g., in this case, halogenated Pt salts). A positive bronchial responsiveness test with hexachloroplatinate provides a definitive diagnosis of halogenated Pt salt sensitivity; however, since bronchial responsiveness can occur in the absence of an IgE-mediated response, a positive response does not provide information on the mechanism of sensitization. SPTs are routinely performed to diagnose sensitivity to specific halogenated Pt salts. Unlike bronchial responsiveness, which involves several mechanisms and may occur in the absence of an IgE-mediated mechanism, SPTs only detect Type I, IgE-mediated sensitization. Results of a study by Merget et al. (1991) show that the Pt SPT response does not always predict the respiratory response to inhaled hexachloroplatinate. The data also support the hypothesis that a non-IgE mechanism may be involved in the response of some individuals, based on the finding that positive hexachloroplatinate bronchial challenge was observed in a few workers testing negative for hexachloroplatinate in the SPT.

4.1.2.1.2. ***Toxicity of soluble forms of Pt: epidemiologic evidence of Pt allergic sensitization.*** Five epidemiologic studies provide information on the characteristics of exposure-response relationships for the development of halogenated Pt salt sensitivity in Pt refinery workers

(Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990) and Pt catalyst production workers (Merget et al., 2000; Linnett and Hughes, 1999). Studies are described in more detail, as follows, and are evaluated for use in developing an RfC for chronic inhalation exposure to halogenated Pt salts (see Sections 4.6 and 5.2). Although there are numerous additional reports of occupational exposure that provide strong supportive evidence for respiratory and sensitization effects of inhaled Pt compounds, exposure measurements or quantitative estimates of exposure were not reported in these studies (Watsky, 2007; Cristaudo et al., 2005; Merget et al., 2002, 2001, 1999, 1996, 1995, 1994, 1991, 1988; Raulf-Heimsoth et al., 2000; Santucci et al., 2000; Newman Taylor et al., 1999; Calverley et al., 1999, 1995; Niezborala and Garnier, 1996; Venables et al., 1989; Biagini et al., 1985a; Jarabek et al., 1984; Dally et al., 1980; Hughes, 1980; Cromwell et al., 1979; Cleare et al., 1976; Harris, 1975; Hunter et al., 1945; Milne, 1970; Parrot et al., 1969; Roberts, 1951). Since data from these studies do not allow for characterization of the shape or slope of the dose-response relationship for halogenated Pt salt sensitivity, additional details on these studies are not summarized in this report.

Bolm-Audorff et al. (1992): Pt Refinery Workers

A cross-sectional study of the employees of a Pt refinery in Germany used a cohort of 65 subjects (63 men and 2 women) that was divided into three exposure categories (high, moderate, and low) on the basis of predicted Pt exposure level (Bolm-Audorff et al., 1992). The mean age of the staff was 37.2 years (SD = 10.8 years), and mean duration of employment (i.e., exposure to Pt) was 8.9 years (range 1–40 years). Exposure categories were defined based on the job location of workers, rather than personal air monitoring data. The high-exposure category consisted of 21 workers in the Pt refinery division of the plant. The moderate-exposure category consisted of 21 workers involved in the refining of gold, silver, palladium, iridium, and osmium, but not Pt. These workers were expected to have been exposed to Pt as "bystanders" because the refining of these other metals took place in the same building as the refining of Pt. The low-exposure category comprised 21 tradesmen and employees involved in alkaline dissolution of metallic Pt. Analysis of Pt in total dust was conducted in 1984 and 1986 using two 3.5-hour stationary monitors. The location of the stationary monitors was identified as the "separation plant"; however, the location of the monitors relative to the work areas that define the exposure groups was not indicated in the study report. The report also did not indicate the number or frequency of measurements taken. Analysis of two 3.5-hour stationary air monitor readings of Pt in total dust in 1984 showed soluble Pt concentrations <0.20 μg soluble Pt/m^3 (the detection limit). In 1986, two 2-hour measurements revealed soluble Pt concentrations of 0.08 and 0.10 μg soluble Pt/m^3. Two 1-hour personal air-monitoring measurements, taken from filter press workers in 1986, showed soluble Pt concentrations of <0.05 μg soluble Pt/m^3 (detection limit) in total dust. The study report did not indicate if the two filter press workers were included in the study, or the location of the "filter press" relative to the three exposure locations. The study

report also did not indicate the chemical analytical methods used to determine air concentrations of total or soluble Pt and made no mention of particle sizes in the air samples. No information was provided regarding the chemical species present or further characterization of Pt beyond the soluble Pt reported. Bolm-Audorff et al. (1992) reported that plant records indicated that the plant was in long-term compliance with the German regulatory exposure standard (8-hour time-weighted average [TWA]) of 2.0 μg soluble Pt/m^3.

Occupational and nonoccupational histories were collected by questionnaire, including the presence of allergy symptoms (conjunctivitis, rhinitis, coughing/expectoration, and respiratory distress). Measures of lung function (FEV_1 and $FEF_{25–75}$) and pulmonary resistance were recorded before and after a Monday shift as well as after the following Friday shift. Assays for nonspecific allergy symptoms and specific allergic sensitization to halogenated Pt salts included a SPT with six common allergens and 10^{-3} *M* the halogenated Pt salt dipotassium hexachloroplatinate (K_2PtCl_6). Levels of serum IgE and Pt-specific IgE were determined, as was histamine release from whole blood following incubation with K_2PtCl_6. Prevalence data were analyzed using χ^2-tests, and mean values were compared using t-tests. Lung function data at different times were compared using the Wilcoxon test for matched pairs. Results of the symptom and medical exams are presented in Tables 4-1 and 4-2, respectively.

Table 4-1. Prevalence of allergic symptoms

Symptoms	High exposure	Moderate exposure	Low exposure
Work-related	11/21[b]	1/23	3/21
Non-work-related[a]	2/21	5/23	3/21
No symptoms	8/21[b]	17/23	15/21

[a]Non-work-related symptoms were judged as such if they also occurred at home.
[b]$p < 0.01$ compared to either the moderate- or low-exposure groups; no estimates of workplace air Pt concentrations experienced by the high-, moderate-, and low-exposure groups of workers were available.

Source: Bolm-Audorff et al. (1992).

Table 4-2. Pt specific and nonspecific allergic results

Endpoint	Symptom status		
	Work-related	Non-work-related	No symptoms
SPT—K_2PtCl_6	9/14[a]	2/10	1/40
SPT—other allergens	2/13	4/10	13/40
Total IgE (U/mL)	230.4 ± 296.9[b, d]	48.6 ± 35.4	108.2 ± 138.5
Pt-specific IgE (percent binding)	10.8 ± 11.3[c]	2.4 ± 1.3	4.6 ± 3.6
Histamine release (percent of maximum)	17.3 ± 20.9	15.6 ± 12.5	19.0 ± 14.8

[a]$p < 0.01$ compared to either the "non-work-related" or "no symptoms" columns.
[b]$p < 0.05$ compared to the "non-work-related" column.
[c]$p < 0.05$ compared to either the "non-work-related" or "no symptoms" columns.
[d]The study report did not indicate if values were reported as means ± SD or means ± SE.

Source: Bolm-Audorff et al. (1992).

Symptoms (including conjunctivitis, rhinitis, coughing, and respiratory distress) assessed as work-related by the subjects were reported significantly more often in the high-exposure category, compared to the moderate- or low-exposure categories (Table 4-1). Allergic symptoms assessed by subjects as non-work-related (also including conjunctivitis, rhinitis, coughing, and respiratory distress) did not occur more frequently in the high-exposure category, compared with the lower exposure categories. In subjects with work-related symptoms, the average latency between the initial exposure and the appearance of symptoms was 4.8 years (SD = 3.9 years, range = 1–13 years). Latencies were not different between different symptom types. Positive Pt SPT results were more frequent in the group with work-related symptoms (Table 4-2). Subjects with work-related symptoms showed sensitivity to environmental allergens less frequently than did those without work-related symptoms. Mean levels of total and Pt-specific IgE were higher in the group with work-related symptoms. Lung function tests in employees exposed to Pt salts with work-related symptoms showed normal function on Monday morning. In the course of the Monday work shift and work week, there was a significant fall in FEV_1 from 100.7 to 95.9% of the predicted values, and other respiratory flow values were similarly affected, most notably FEF_{25}, which fell to 95.1 and 73.4% of the predicted values by Monday and Friday after shift, respectively. Measures of airway resistance remained unchanged.

This study reports the occurrence of cases of allergic sensitization to halogenated Pt salts in a workplace in which air concentrations of soluble Pt appeared to have been below the German occupational exposure limit of 2 μg soluble Pt/m^3 (8-hour TWA), although details of the methods used to measure Pt and to determine "soluble" Pt were not included in the study report. The maximum reported concentration among the limited number of air samples collected from the workplace was 0.1 μg soluble Pt/m^3. However, the exposure data are too limited to reliably estimate the air concentrations experienced by the three exposure categories of workers and personal air monitoring was only done for a 1-hour period for two filter press workers. Thus, no

characterization of the shape or slope of the exposure-response relationship for development of allergic sensitization to halogenated Pt salts was provided, and a no-observed-adverse-effect level (NOAEL) for allergic sensitization to halogenated Pt salts was not identified. The characterization of Pt allergic sensitization did not include specific respiratory challenge to Pt or nonspecific respiratory challenge, but did include basic lung function, Pt-specific and total IgE, histamine release, and SPT to the halogenated Pt salt hexachloroplatinate. In addition, important factors, such as smoking status and years of exposure, were apparently not included in the analysis.

Linnett and Hughes (1999): Pt Refinery and Catalyst Production Workers

In a retrospective study of medical surveillance data collected over a 20-year period at a Pt processing company in the United Kingdom (Linnett and Hughes, 1999), the allergenicity potentials of two soluble Pt forms, halogenated Pt salts (chloroplatinates) and tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$), were studied in workers involved in three different operations at the same site. Workers in the Pt group metal refinery area were chemical process operators (CPO, n = 270) who refined Pt and other PGEs from ore using processes involving concentrated HCl dissolution, ammonium hexachloroplatinate precipitation, and thermal reduction of hexachloroplatinate to Pt metal. Soluble Pt in air samples from the refinery area were reported to consist solely of chloroplatinates. No data on Pt speciation were provided to substantiate that Pt exposure in the refinery area was restricted to chloroplatinates. Workers in the tetraamine Pt dichloride lab (n = 31) made tetraamine Pt dichloride from chloroplatinic acid in a closed reactor vessel to ultimately produce a dry powder of tetraamine Pt dichloride. Operations with the dust were carried out with respiratory protection. Soluble Pt in air samples was considered by the authors to contain both chloroplatinates and tetraamine Pt dichloride. No data on Pt speciation were provided to substantiate that Pt exposure in the tetraamine Pt dichloride lab included both chloroplatinates and tetraamine Pt dichloride. Workers in the third area (n = 39) made automobile catalysts by impregnating a coated substrate with a solution rich in tetraamine Pt dichloride and other PGE elements and firing the material to attain thermal reduction to the elemental metals. The authors state that tetraamine Pt dichloride was expected to be the only soluble Pt form to which the automobile catalyst workers were exposed. No Pt speciation data were provided to substantiate that tetraamine Pt dichloride was the only form of Pt present. Air samples were collected by personal air monitoring in work areas (see Table 4-3). The frequency of sampling was not reported. Sampling times in the refinery work areas were reported as "short", but not otherwise specified. For the other two work areas, samples were collected for an entire shift and reported as an 8-hour TWA. Samples were collected on a 25-mm filter with a 7-hole sampling device equipped with a pump (2 L/minute). Filters were dissolved in 0.12 M HCl and analyzed for soluble Pt by electrothermal atomic absorption spectrophotometry. More specific chemical analysis to identify the soluble Pt forms in the air samples was not mentioned.

Information regarding particle sizes in the air samples was not provided. Sensitization was defined as one or more of the following: (1) a repeatable positive SPT to Pt compounds including $(NH_4)_3PtCl_6$, Na_2PtCl_6, Na_2PtCl_4, and tetraamine Pt dichloride, (2) a positive "specific" bronchial challenge test (the study report did not indicate the test substance used, although "specific" implies a chloroplatinate salt), (3) work-related symptoms and assessment by an occupational physician, or (4) a positive patch test. SPTs were conducted with two halogenated Pt salts [$(NH_4)_2PtCl_6$ and Na_2PtCl_6] and tetraamine Pt dichloride at concentrations of 10^{-3} g/mL, and the positive criteria was a weal diameter ≥2 mm of vehicle control (glycerol carbol saline). If a negative Pt SPT was obtained in a worker presenting with symptoms, FEV_1 and FEF variables were measured to ascertain a relationship with work. One symptomatic worker who was Pt SPT negative was diagnosed as sensitized with a specific bronchial challenge test. No mention was made in the report of operational details of the patch test or of the actual use of this test in diagnosing a case of sensitization.

Table 4-3. Pt sensitization in CPO workers and exposure to different soluble Pt compounds in different work environments

	Pt group metal refining	Tetraamine Pt dichloride synthesis	Catalyst production
Number of subjects	270 (257 men; 13 women)	31 (31 men; 0 women)	39 (39 men; 0 women)
Number of sensitization cases	106	5	0[e]
Median latency[a] to sensitization (mo)	12.6	36.9	Not applicable
Latency range (mo)	1.0–107.9	7.1–51.7	Not applicable
Chemical exposure[b]	chloroplatinates only	chloroplatinates and tetraamine Pt dichloride	tetraamine Pt dichloride only
Total number of air samples collected[c] (personal air monitoring)	380	130	176
Soluble Pt concentration	Number of samples in range (collected between 1989 and 1991)		
<0.5 µg soluble Pt/m^3 [d]	335 (88%)	67 (52%)	107 (61%)
0.5–<1.0 µg soluble Pt/m^3	21 (6%)	12 (9%)	38 (22%)
1.0–<2.0 µg soluble Pt/m^3	15 (4%)	14 (11%)	16 (9%)
2.0–<5.0 µg soluble Pt/m^3	7 (2%)	25 (19%)	10 (6%)
5.0–<10.0 µg soluble Pt/m^3	1 (<1%)	9 (7%)	2 (1%)
>10.0 µg soluble Pt/m^3	1(<1%)	3 (2%)	3 (2%)

[a]Number of months between initial exposure and development of sensitization.
[b]Pt compounds in the work environment in the different areas of the refinery were determined by work conditions. No data were provided that demonstrate specific Pt compounds and measurement of Pt concentrations in each work area are only reported as "airborne soluble platinum"; no further speciation data were provided. However, the authors state that exposure in the refinery was restricted to chloroplatinates, that the tetraamine Pt dichloride lab was a mixed exposure to chloroplatinates and tetraamine Pt dichloride, and that the catalyst production area was to tetraamine Pt dichloride only.
[c]Sampling times in the refinery work areas were reported as "short", but not otherwise specified. For the other two work areas, samples were collected for an entire shift and reported as an 8-hour TWA.
[d]Concentrations in these groups of samples were reported only as <0.5 µg soluble Pt/m^3. No information on detection limit was provided.
[e]SPTs were performed using $(NH_4)_2PtCl_6$, Na_2PtCl_6, Na_2PtCl_4, and tetraamine Pt dichloride.

Source: Linnett and Hughes (1999).

Air sampling (8-hour TWA concentrations) and prevalence data for allergic sensitization (for CPO workers only) are given in Table 4-3. Although demographic data concerning age and smoking habits were reported, as well as the medians and ranges of the time to diagnosis for the cases of allergic sensitization, no information on the duration of employment for the workers in the three groups was provided. The results demonstrate a high prevalence of Pt salt sensitivity (106 sensitized/270 CPO workers [39%]) in a workplace in which chloroplatinates were described as being likely to be the only soluble Pt forms present. The 270 CPOs were the most heavily exposed workers in the Pt group metal refining area; an additional 136 workers (these workers are not included in the 270 CPOs) in the refining area who were expected to have much

less exposure showed a lower prevalence of allergic sensitization (4/136, 3%). In the combined group of 406 chloroplatinate workers (270 CPOs and 136 non-CPOs), 110 cases of halogenated Pt salt allergy were identified, with 100 testing positive by SPT to halogenated Pt salts. Among the 10 cases with a negative Pt SPT, 1 was positive in a patch test, 1 was positive in a "specific" bronchial challenge test (the test substance was not identified in the study report), 1 had work-related upper respiratory symptoms, and 7 had bronchospasms at work. The study did not report the Pt SPT results for the 270 CPO group, although 106/270 were reported as sensitized. Personal air monitoring data in the refining work area indicated that the occupational limit of 2.0 μg soluble Pt/m^3 was exceeded in only 9/380 samples (2%) collected over a 2-year period (Table 4-3). In contrast, soluble Pt concentrations exceeded 2.0 μg/m^3 in 37/130 samples (28%) collected from the tetraamine Pt dichloride synthesis area (where tetraamine Pt dichloride was expected to be the predominant soluble Pt form) and 5/31 CPO workers showed Pt salt sensitization (16%). No cases of sensitization (to either halogenated Pt salts or tetraamine Pt dichloride) occurred in the 39 catalyst production workers, whose exposure to soluble Pt was expected to have been restricted to tetraamine Pt dichloride. Soluble Pt concentrations exceeded 2.0 μg/m^3 in 15/176 samples (9%) in this catalyst production area where exposure was expected to be limited to tetraamine Pt dichloride. The cumulative probability of sensitization for a 5-year period was 51% in CPOs classified by the authors as exposed to chloroplatinates alone, 33% in tetraamine Pt dichloride lab workers (classified as exposed to a mix of chloroplatinates and tetraamine Pt dichloride), and 0% in workers classified as exposed to tetraamine Pt dichloride alone (i.e., catalyst production workers). The study authors concluded that tetraamine Pt dichloride may not be allergenic, although the limited number of workers who were classified as exposed to tetraamine Pt dichloride alone (n = 39) and the lack of information on duration of employment limits the confidence in this conclusion.

Atopics were excluded from employment as CPOs in the Pt processing company; therefore, atopy could not be evaluated as a risk factor for development of halogenated Pt salt sensitization. There was no evidence of an effect of age at the start of employment as a risk factor; however, smoking was a risk factor for the development of halogenated Pt salt sensitization. For workers in the Pt group metal refining area (classified as exposed to chloroplatinates alone), smokers of 1–19 cigarettes/day were 2.19 times more likely to develop halogenated Pt salt sensitization ($p < 0.01$) and smokers of ≥20 cigarettes/day had 3.24 times higher risk ($p < 0.001$) relative to nonsmokers. Data for the relative risk of smokers to nonsmokers in the tetraamine Pt dichloride lab (classified as mixed exposure to chloroplatinates and tetraamine Pt dichloride) were not provided. The relative risk of developing Pt sensitization was significantly lower (0.33 relative risk; 0.14–0.78 95% CI) for workers in the tetraamine Pt dichloride lab relative to the workers in the Pt group metal refining area if smoking was not considered. When adjusted for smoking, the relative risk of developing Pt sensitization did not

differ between workers in the tetraamine Pt dichloride lab and the Pt group metal refining area (0.47 relative risk in the tetraamine Pt dichloride lab; 0.20–1.12 95% CI).

Data from this study do not characterize the shape or slope of the exposure-response relationship for halogenated Pt salt allergic sensitization and do not identify a NOAEL (an exposure level to a pertinent soluble Pt form that produced no cases of sensitization). A key limitation to the usefulness of this study for developing a chronic inhalation RfC is that, although median latencies to sensitization were reported for the refining and tetraamine Pt dichloride synthesis workers, no information was provided concerning the duration of employment of the workers in any of the three groups. However, the results clearly show that workplace air concentrations of chloroplatinates, predominantly <0.5 µg soluble Pt/m^3 (the reported air concentration for 335/380 or 88% of collected air samples from the refining area), were associated with a very high prevalence of workers who developed allergic sensitization, and they provide limited evidence that tetraamine Pt dichloride may not be allergenic. Because airborne soluble Pt concentrations were reported as number and percent of samples above and below 0.5 µg soluble Pt/m^3 rather than actual concentrations, there are no data on the actual concentration of samples below 0.5 µg soluble Pt/m^3. The characterization of Pt sensitization included specific respiratory challenge and diagnosis of Pt-related symptoms at work by a physician as Pt-specific SPT to halogenated Pt salts ($[NH_4]_2PtCl_6$, Na_2PtCl_6, and Na_2PtCl_4) and tetraamine Pt dichloride.

Baker et al. (1990); Brooks et al. (1990): Pt Refinery Workers

A cross-sectional health examination evaluating workers for halogenated Pt salt allergy was conducted in 1981 in workers in a U.S. precious metals reclamation plant (Baker et al., 1990, Brooks et al., 1990). Workers were administered a medical questionnaire for symptoms of the eyes (symptoms were not specified), nose (itchy and/or runny nose), chest (wheeze, cough, shortness of breath, chest tightness), and dermatitis (symptoms were not specified); use of a severity scale in this survey was not reported. Physical examinations of workers included spirometry (forced vital capacity [FVC], FEV_1, FEV_1/FVC) before and after a work shift, cold air bronchial inhalation challenge (measuring the post-challenge change from baseline for FEV_1 following inhalation of cold air), and skin prick testing to halogenated Pt salts (sodium hexachloroplatinate [Na_2PtCl_6] and ammonium hexachloroplatinate [$(NH_4)_2$ $PtCl_6$]) and three common aeroallergens (ragweed, timothy, and dust). Serum concentrations of total IgE and IgE specific for halogenated Pt salts were measured by a radioallergenosorbent test (RAST). The plant had been in operation for about 13 years at the time of the study in 1981 (e.g., from approximately 1968 to 1981). The subjects included 107 of the 123 employees in 1981 ("current workers") and 29 former employees. Medical records for the plant indicated that 49 workers had been terminated from 1971 to 1979 due to suspected halogenated Pt salts allergy; the 29 former workers in the study were among the 49 medically terminated workers. The latencies between

employment termination and the 1981 medical examination were 7–107 months (average = 5 years). The current workers had a mean age of 33.7 years and a mean duration of employment of 70.8 months (SDs or ranges for these means were not reported): 99 were men and 8 were women; 65% were current or ex-smokers. The terminated workers (28 men and 1 woman) had a mean age of 36.5 years and a mean duration of employment of 61.2 months; 97% were current or ex-smokers.

"Pt salt concentrations" were reported (as an 8-hour TWA) for air samples collected in a number of work areas by the company during several workdays between 1977 and 1979; the number of sampling days varied with sampling location and ranged from 1 to 9 days. The air samples were collected by stationary air sampling techniques; personal air samples for workers in this study were not collected. The study report did not specify the analytical methods used to determine the Pt salt concentrations in the collected air samples or report the LOD. No mention of acid extraction of filters or detection systems was made. Requests for more information on the air sampling and analytical techniques were sent to the study authors in March 2005, but no replies were received within 1 year of that request. Under the assumption that Pt salt concentrations reported were soluble Pt, analysis of Pt salt concentrations in workplace air samples indicated that 50–75% of the samples in several work areas exceeded the OSHA TWA permissible exposure limit (2.0 μg soluble Pt/m^3). The geometric mean air concentrations of Pt salts (with number of sampling days, n, indicated in parentheses) in the recovery, recovery/sampling, refinery, refinery tray, and warehouse areas were 5.3 (n = 9), 2.7 (n = 4), 10.7 (n = 3), 27.1 (n = 4), and 8.6 (n = 8) μg soluble Pt/m^3, respectively, compared with values of 0.5 (n = 1), 0.4 (n = 3), and 0.6 (n = 3) μg soluble Pt/m^3 in the residue, analytical laboratory, and administrative office air conditioning unit areas, respectively (Baker et al., 1990). SDs or ranges for these means were not reported; thus, measures of the variability of Pt salt concentrations in the air samples are not available.

Positive SPT results to halogenated Pt salts (Na_2PtCl_6 or $[NH_4]_2PtCl_6$ concentrations ranging from 10^{-9} to 10^{-3} g/mL) were found in 23 workers (17% overall; 15/107 current workers [14%] and 8/29 terminated workers [28%]), compared with 1 positive result in 45 control subjects who were University of Cincinnati employees. The control subject showing a positive SPT to either halogenated Pt salt was a scientist who had worked with Pt salts in the past; the other control subjects had no known exposure to Pt salts. Among current workers, positive Pt SPT results occurred in all areas of the facility except the administrative offices (Table 4-4). The occurrence of sensitization to halogenated Pt salts was correlated with mean air concentrations in the current employees' work areas (Spearman correlation = 0.71; $p = 0.11$), but not to a statistically significant degree using a significance criterion of $p < 0.05$. However, a logistic regression analysis indicated that the risk of a positive SPT to Pt was statistically significantly increased ($p = 0.01$) 1.13 times with 1-μg/m^3 increments in exposure concentration (the report did not specify if adjustment for smoking was made in this analysis).

Table 4-4. Incidences of positive hexachloroplatinate SPT results among current workers in different work areas in a U.S. precious metal reclamation facility in 1981

Work area	Mean air concentration[a] (μg Pt/m^3 as Pt salts)	Incidence of workers with positive Pt SPT
Residue/recovery	0.5/5.3	1/15 (7%)
Refinery	10.7	2/14 (14%)
Refinery, tray area	27.1	2/3 (67%)
Chemical products/salts	Not reported[b]	3/22 (14%)
Analytical laboratories	0.4	2/19 (11%)
Warehouse/stores	8.6	1/3 (33%)
Maintenance	Not reported[b]	3/12 (25%)
Manager/office	0.6	0/15
Other (electrician, boiler operator)	Not reported[b]	1/4 (25%)
Total		15/107 (14%)

[a]Geometric means of 8-hour TWA concentrations measured with stationary sampling devices during 1–9 sampling days between 1977 and 1979 (see text). SDs or ranges for these means were not reported.
[b]Air concentrations for these work areas were not reported and apparently were not measured.

Sources: Baker et al. (1990); Brooks et al. (1990).

Results of the symptoms survey, pulmonary function test, cold air challenge, aeroallergen test, and total IgE analysis by Pt SPT result (positive or negative) and work status (current or former) are summarized in Table 4-5. Current workers with positive SPT results for halogenated Pt salts were more likely to report rhinitis symptoms, asthma symptoms, or dermatitis, and to display positive results in a cold-air challenge, than current workers with negative SPT results to Pt, as indicated by statistically significantly increased prevalence odds ratios (PORs) for rhinitis symptoms (8.3, 95% CI: 1.8–37.8), asthma symptoms (11.3, 95% CI: 2.3–54.6), reported dermatitis (12.6, 95% CI: 2.2–72.8), and positive cold-air challenge (7.7, 95% CI: 1.5–38.3) (Baker et al., 1990). In addition, among current workers, current or past smokers were more likely to have a positive SPT result for halogenated Pt salts than nonsmokers (POR = 9.0, 95% CI: 1.2–69.3).

Table 4-5. Symptoms, test results and relative risk of symptoms by Pt SPT result

Symptom or test result	Current workers		Former workers		POR[a]
	Incidence in workers with positive Pt SPT	Incidence in workers with negative Pt SPT	Incidence in workers with positive Pt SPT	Incidence in workers with negative Pt SPT	
Rhinitis symptoms	13/15 (87%)	33/92 (37%)	3/8 (38%)	7/21 (33%)	8.3 ($p = 0.001$)
Asthma symptoms	10/15 (77%)	18/92 (22%)	4/8 (50%)	8/21 (40%)	11.3 ($p = 0.001$)
Reported dermatitis	5/15 (33%)	8/92 (9%)	2/8 (25%)	4/21 (19%)	12.6 ($p = 0.001$)
$FEV_1/FVC < 70\%$	2/15 (13%)	4/92 (5%)	4/8 (50%)	1/21 (5%)	1.9 ($p = 0.52$)
Positive cold air challenge	5/15 (33%)	6/92 (7%)	4/8 (50%)	4/21 (19%)	7.7 ($p = 0.003$)
Elevated total IgE	4/15 (27%)	7/92 (8%)	5/8 (63%)	4/21 (19%)	3.5 ($p = 0.54$)
Positive aeroallergen SPT[b]	6/15 (40%)	29/92 (32%)	2/8 (25%)	6/21 (29%)	1.5 ($p = 0.01$)

[a]Prevalence odds ratio (POR) of positive versus negative Pt SPT workers (current workers only), adjusted for aeroallergen test status and smoking (current, past, or never).
[b]Aeroallergens tested were ragweed, timothy, and dust.

Source: Baker et al. (1990).

Results of the RAST analysis for Pt-specific IgE showed Pt-specific RAST binding (expressed as a percentage of total IgE) in sera of positive and negative Pt SPT workers of 7.0 ± 1.4 and 4.3 ± 0.7% (means ± standard error [SE], $p < 0.001$), respectively; the value in eight control volunteers was 4.2 ± 0.8%. According to the study authors, using a value of two SEs above the mean in control volunteers to define an abnormal value (e.g., a value of 5.8%), 20 of 22 positive Pt SPT workers had abnormal RAST values, compared to 8 of 94 negative Pt SPT workers (Brooks et al., 1990). PORs for the RAST analysis were not reported. Results of the RAST analysis on a subset of the current (13/15) and former (6/8) workers with positive Pt SPT were also reported by Biagini et al. (1985a); however, at the time of the Biagini et al. (1985a) study, samples from all workers were not available for analysis.

In 1982, SPTs for halogenated Pt salts were repeated in 74 of the 107 current workers and 12 of the 29 medically terminated workers (Brooks et al., 1990). The 12 medically terminated workers showed the same results in 1981 and 1982: 5 were negative and 7 were positive. Among the 74 "current workers" who were evaluated in 1981 and 1982, 7 showed positive Pt SPT results in 1981. In 1982, these 7 workers still had positive Pt SPT results, and an additional 5 workers also had positive Pt SPT results (i.e., 5 of the 67 subjects with negative results in 1981 were converted to Pt SPT sensitive in 1982).

The results from this cross-sectional health examination of workers in a U.S. Pt refinery (Baker et al., 1990; Brooks et al., 1990) provide strong evidence that exposure to halogenated Pt salts in workplace air increases the risk of allergic sensitization and associated respiratory and dermal symptoms. The follow-up results (Brooks et al., 1990) are consistent with those of Merget et al. (1999, 1994), suggesting that allergic symptoms and Pt SPT sensitivity do not necessarily disappear following removal from exposure. The cross-sectional design limits the usefulness of the results for developing an RfC for halogenated Pt salts. Although work-area air concentrations were measured for the 15 office workers who were found to be nonsensitized, the cross-sectional design does not allow assessment of the subsequent health status of these workers or the status of office workers who may have left the workplace before the survey. Thus, a reliable NOAEL for halogenated Pt salt allergic sensitization was not identified in this study. In addition, the characterization of Pt sensitization was largely based on SPT to hexachloroplatinate and did not include specific respiratory challenge to hexachloroplatinate. Data included nonspecific respiratory challenge to cold air, basic lung function, Pt-specific and total IgE, histamine release, SPT to common aeroallergens, and smoking status.

Merget et al. (2000): Catalyst Production Workers

A prospective cohort study was conducted between 1989 and 1995 in a catalyst production plant in Germany (Merget et al., 2000); additional details of the study are also reported in Merget (2000) and Rosner and Merget (2000). The study initially enrolled 166 subjects, and over the 5-year period, added 142 new employees. Over the course of the study, 308 subjects were recruited, 98 either refused to participate or left the study, and 4 were excluded from the study because of a positive SPT to the halogenated Pt salt, hexachloroplatinate. Over the approximate 5-year study period, the number of employees who had at least two study examinations was 275. Using a system based on job location and title, subjects were grouped into four exposure categories: high- (n = 115), persistent-low- (n = 51), intermittent-low- (n = 61), and no-exposure (n = 48) (see Table 4-6 for selected demographic data for these exposure groups). The high-exposure category included production line workers and craftsman engaged in maintenance or demolition of production lines. Persistent-low-exposure workers worked within the catalyst production department, but were not in the production lines and included office workers, wash coat preparation workers, and staff involved in quality control, chemical analysis, or the warehouse. Intermittent-low-exposure workers were those who only entered the catalyst production building on an intermittent basis. Workers who never entered the catalyst production building were assigned to the no-exposure control group.

Table 4-6. Summary of selected endpoints in health surveys of catalyst plant workers

		Exposure group			
		High	**Persistent low**	**Intermittent low**	**No**
Group size (n)		115	51	61	48
Age (in years; mean, 95% CI)		32 (30–34)	32 (29–35)	39 (36–42)	38 (35–41)
Males (n, %)		115 (100%)	48 (94.1%)	60 (98.4%)	41 (85.4%)
Smokers (n, %)		53 (46.1%)	16 (31.4%)	18 (29.5%)	16 (33.3%)
Ex-smokers (n, %)		38 (33%)	12 (23.5%)	19 (31.1%)	16 (33.3%)
Nonsmokers (n, %)		24 (20.9%)	23 (45.1%)	24 (39.3%)	16 (33.3%)
Time in plant before first survey[a]		31 (17–45)	72 (49–95)	144 (124–164)	123 (100–146)
Job exposure before first survey[a]		21(15–27)	43 (30–56)	91 (75–107)	
Time between 1st and final survey[a]		33 (29–37)	46 (40–52)	43 (38–48)	39 (33–45)
Exposure (ambient-air) (ng soluble Pt/m^3)	1992	14; 8/41; 16[b]	6.6; 4.2/7.5; 8		0.05; 0.03/0.05; 8
	1993	37; 12/64; 12	0.4; 0.3/1.3; 8		All <0.13; 4
Exposure (personal-air)[c] (ng soluble Pt/m^3)	1993	177; 93/349; 22	Not performed		Not performed
Positive SPT allergen[d]	Initial survey	19	10	13	11
	Final survey	15	13	12	12
Positive SPT - Pt[e]	Initial survey	0	0	0	0
	Final survey	13	1[f]	0	0
Total IgE (kU/mL; mean, 95% CI)	Initial survey	33 (30–90)	36 (31–108)	33 (29–66)	26 (23–66)
	Final survey	37 (33–114)	31 (27–137)	40 (35–121)	34 (29–118)
FEV_1 (% predicted)	Initial survey	101 (99–103)	103 (100–106)	104 (100–108)	106 (102–110)
	Final survey	100 (97–103)	103 (100–106)	102 (98–106)	103 (99–107)
FEV_1 <90% predicted (n)	Initial survey	20	7	14	4
	Final survey	22	9	13	6
Bronchial hyperresponsive-ness dose-response slope[g] (%/mg, 95% CI)	Initial survey	2.3 (2.1–4.2)	1.5 (1.3–3.4)	2.5 (2.2–4.8)	2.5 (2.2–4.9)
	Final survey	2.3 (2.1–3.1)	1.4 (1.2–2.6)	2.1 (1.9–5.1)	2.1 (1.8–5.7)
Bronchial hyperresponsive-ness[g] (number of workers with PD_{15} <1 mg histamine, %)[h]	Initial survey	8 (7.1%)	1 (2.1%)	6 (9.8%)	1 (2.1%)
	Final survey	7 (6.9%)	1 (3.4%)	3 (6.0%)	0
Symptoms[i] before exposure	Initial survey	19	11	14	7
Symptoms after exposure but before study	Non-work[j]	5	6	12	1
	Work	5	2	1	0
Symptoms during study	Non-work	23	3	3	1
	Work	15	3	0	3

[a]Presented as the mean number of months with 95% CI in parentheses.
[b]Presented as the median concentration; lower/upper-quartile concentration and number of samples, as reported.
[c]Personal-air assessments were performed in 1993 only, and only in the high-exposure group.
[d]Allergens used were cat dander, grass and birch pollen, dust mite, and air-borne fungus.
[e]Conversion from negative-to-positive SPT for 10^{-2} M hexachloroplatinic acid.
[f]This subject was misclassified as "low-exposure" and admitted to occasional direct contact with Pt salts.
[g]Bronchial hyperresponsiveness was not assessed in 16 (7%), 13 (12%), and 11 (9%) of workers in the high-, persistent-low-, and intermittent-low-exposure groups, respectively.
[h]PD_{15} is the dose of histamine causing a 15% decreased in FEV_1 in bronchial hyperresponsiveness tests.
[i]Symptoms included wheezing, rhinitis, burning eyes, and dermatitis.
[j]"Non-work" and "work" indicate whether symptoms were work-related.

Source: Merget (2000).

Health surveys of subjects were conducted at several time periods, including initial survey (start of study), at intervals of 6 months during the first year and afterward at yearly intervals including the final survey at the end of the study (most subjects received 4–5 examinations over the course of the study). The mean durations of employment at the time of the initial health survey (with ranges noted in parentheses) were 21 (15–27) months, 43 (30–56) months, 91 (75–107) months, and 123 (100–146) months for the high-, persistent-low-, intermittent-low-, and no-exposure groups, respectively. The mean time between the initial and final survey per subject for the groups (in order of decreasing exposure) were 33 (29–37) months, 46 (40–52) months, 43 (38–48) months, and 39 (33–45) months. Health survey endpoints included self-reported allergic symptoms (shortness of breath/wheezing, rhinitis, conjunctivitis, and dermatitis) with medical follow-up if needed; analysis of serum Pt concentrations; SPTs to five common allergens (cat dander, grass and birch pollen, dust mite, and air-borne fungus) plus the halogenated Pt salt, hexachloroplatinate; lung function tests (FEV_1); bronchial responsiveness to histamine); and total and common allergen-specific serum IgE (by RAST). The primary outcome variable was SPT conversion (SPTC), the change from a negative-to-positive response in the SPT to halogenated Pt salts, which the authors considered evidence of sensitization to halogenated Pt salts. Predictive factors for SPTC were determined using a multivariate model, incorporating exposure category, age, smoking status, atopy, preexisting asthma symptoms, total IgE, FEV_1, and bronchial hyperresponsiveness as well as various employment history variables.

Stationary (work area) exposure assessments were conducted in 1992 and 1993 (Merget, 2000; Merget et al., 2000; Rosner and Merget, 2000). Sampling periods for these assessments varied between 12 and 17 hours. Thus, the reported air concentrations from the stationary air samples represent 12- to 17-hour TWA concentrations. The study author indicated that there were three 8-hour shifts during the 24-hour production in the plant, and therefore, there were no differences between work shifts or workplace activity (email from Dr. Rolf Merget, Research Institute for Occupational Medicine, Institutions for Statutory Accident Insurance and Prevention, University Hospital Bergmannsheil, Ruhr University, Bochum, Germany to Andrew A. Rooney, U.S. EPA, dated September 23, 2008). Total and soluble Pt concentrations were determined by standard methods (either inductively coupled plasma emission spectrometry or graphite furnace AAS); detection limits were 0.025 ng soluble Pt/m^3 in 1992 and 0.13 ng soluble Pt/m^3 in 1993 due to the use of different analytical methods in the 2 years (Merget, 2000). Soluble Pt was defined by the amount of Pt assayed in a 70-mM HCl acid extraction of each sample. Additionally, personal-air sampling assessments were conducted in 1993 in high-exposure subjects. Merget et al. (2000) noted that only 22 personal air measurements were made, indicating that personal air measurements were not made for all workers in the high-exposure category (n = 115 subjects). The sampling period for each personal-air assessment was

8 hours, and the detection limit was reported as "about 20 ng/m^3" (Merget et al., 2000). No information on particle size distribution in the collected samples was reported. No information was provided regarding the chemical species present or further characterization of Pt beyond the soluble Pt reported.

Results for the exposure assessments and selected endpoints are presented in Table 4-6. The ratio of total to soluble Pt was reported to be approximately 10:1 in most air samples. In the catalyst production area (high-exposure), the numbers of samples collected in 1992, 1993, and the 1993 personal-air assessment were 16, 12, and 22, respectively. Median concentrations (with lower- and upper-quartile values noted in parentheses) for the stationary air samples from the high-exposure catalyst production areas were 0.014 (0.008, 0.041) μg soluble Pt/m^3 in 1992 and 0.037 (0.012, 0.064) μg soluble Pt/m^3 in 1993 (Merget, 2000). Median (and lower- and upper-quartile) concentrations in personal air samples were markedly higher: 0.177 (0.093, 0.349) μg soluble Pt/m^3 (Merget, 2000). For the low-exposure areas (subjects in the persistent-low and intermittent-low groups), median (and lower- and upper-quartile) concentrations were 0.0066 (0.0042, 0.0075) μg soluble Pt/m^3 in 1992 and 0.0004 (0.0003, 0.0013) μg soluble Pt/m^3 in 1993. The maximum concentrations in the low-exposure areas were 0.0086 μg soluble Pt/m^3 in 1992 and 0.0015 μg soluble Pt/m^3 in 1993 (Merget and Rosner, 2001). For the no-exposure areas, median concentrations (and lower and upper quartiles) were 0.00005 (0.00003, 0.0005) μg soluble Pt/m^3 in 1992 and all values were <0.00013 μg soluble Pt/m^3 in 1993 when a different detection system was used. Concentrations of soluble Pt in stationary and personal-air samples were highly variable: 100- and 1,000-fold ranges of soluble Pt concentrations were recorded in the stationary and personal-air samples collected in the high-exposure group, respectively. The threshold limit value (TLV) of 2.0 μg/m^3 was exceeded in 3 of the 78 total exposure measurements made; all three were recorded in the personal-air sampling assessments in the catalyst production (high-exposure) area. Since only 22 personal air measurements were made (e.g., measurements were not made for all 115 workers in the high-exposure category), data that would allow analysis for a correlation between individual personal air monitoring data and sensitization outcome do not appear to have been collected by Merget et al. (2000).

Merget et al. (2002) reported results of the sera analysis for Pt and examined the relationship of Pt concentration in sera to allergy outcome. A total of 38 measurements of Pt in sera were made from six workers; three workers from the high-exposure group with SPT conversion to halogenated Pt salts and three workers from the low- or no-exposure groups with no SPT conversion to halogenated Pt salts. Blood samples for analysis were obtained 5–8 times during the 5-year study. Sera Pt was measured by adsorptive voltammetry, with a detection limit of 0.2 ng/L. Merget et al. (2002) found no correlation between Pt concentrations in sera with allergy outcome.

The percentage of smokers was higher (approximately 46%) in the high-exposure category compared to the low- and no-exposure groups (approximately 30–33%). Based on the

incidence of positive SPT to non-Pt allergens at the initial survey, the incidence of atopy was similar across all three categories, with positive SPT to non-Pt allergens in 19/115 (16.5%), 10/51 (19.6%), and 13/61 (21.3%) workers in the high-, persistent low- and intermittent low-exposure groups, respectively. At the beginning of the study, all subjects were Pt SPT-negative (Table 4-6). SPTC occurred (n = 13; 11.3% of subjects) only in the high-exposure category. Of these 13 subjects, 10 were newly hired employees and 3 had been employed for 68, 16, and 10 months prior to the initial survey. Nine of the 13 subjects showed SPTC during the third year of the follow-up; the remaining showed SPTC during years 1, 2, 4, and 5 after the initial survey (incidence of SPTC was 4.1 per 100 person-years, and slightly higher for newly employed subjects). One subject in the low-exposure category did show SPTC conversion, but this subject was found to be misclassified as to exposure category after admitting to performing occasional high-exposure tasks. Due to the uncertainty surrounding this misclassified worker, they were not considered further. Work- and non-work-related new allergy symptoms occurred more frequently in the high-exposure category (Table 4-6). No subject with a negative Pt SPT and new symptoms showed a positive Pt SPT upon follow-up exam. The study authors reported that results of pulmonary function tests (FEV_1 percent of predicted), bronchial hyperresponsiveness tests (dose-response slope and number of workers with a PD_{15} <1 mg histamine), and total IgE did not differ between exposure categories (Table 4-6).

The multivariate analysis showed a strong association ($p = 0.011$) between exposure and SPTC; less-pronounced associations with SPTC included smoking ($p = 0.054$), total IgE ($p = 0.036$), and FEV_1 (percent predicted) ($p = 0.041$) (Merget et al., 2000). Age-adjusted relative risks for developing a positive Pt SPT in the high-exposure category were elevated for smokers compared with nonsmokers and ex-smokers (odds ratio = 3.9, 95% CI = 1.6–9.7). Age-adjusted relative risks for developing a positive Pt SPT in the high-exposure category were not elevated for individuals with lower FEV_1 values (below 90% of predicted value; odds ratio = 1.1, 95% CI = 0.7–1.3) or with elevated total IgE (>100 kU/L; odds ratio = 1.1, 95% CI = 0.8–1.6). Intervention procedures prevented determining how many subjects with SPTC developed allergic symptoms. Neither atopy, bronchial hyperresponsiveness (slope), nor pre-existing asthma were significantly predictive for halogenated Pt salt sensitization.

The Merget et al. (2000) prospective health survey of workers in a catalyst production plant provides information on the relationship between exposure to chloroplatinates and the development of allergic sensitization to halogenated Pt salts. Merget et al. (2000) state that the concentration of soluble Pt in the low-exposure group areas may be defined as "safe" because no cases of Pt-specific allergic sensitization were observed in workers in these areas. No cases of sensitization occurred in the 5-year period in 111 workers ("persistent" and "intermittent" low groups) who worked in areas with median concentrations of 0.0066 µg soluble Pt/m^3 in 1992 and 0.0004 µg soluble Pt/m^3 in 1993. Therefore, the exposure concentration in the low-exposure areas represents a NOAEL, although the authors do not use that language. There was 1 subject

in the original 112 workers in this group who became sensitized, but the subject admitted to occasional direct contact with Pt salts (see Table 4-6). Merget et al. (2000) is the only study among the available epidemiologic studies on allergic sensitization to halogenated Pt salts with a prospective design. Consistent with the superior detection capabilities of prospective designs compared with cross-sectional or retrospective designs, the study identified the lowest exposure level associated with a statistically significant increased prevalence of sensitized subjects (i.e., the lowest-observed-adverse-effect level [LOAEL]): 13/115 catalyst production ("high-exposure") workers developed Pt-specific allergic sensitization in the 5-year period. Median concentrations in stationary air samples in the catalyst production area were 0.014 and 0.037 μg soluble Pt/m^3 in 1992 and 1993. The median value for personal air monitoring data was 0.177 μg soluble Pt/m^3, suggesting that stationary air sampling may have underestimated exposure in this work area. A multivariate analysis of explanatory variables for SPTC found that, in addition to exposure category, smoking, total IgE, and FEV_1, were statistically significant variables. Smokers in the high-exposure group showed a significantly elevated, age-adjusted risk for developing sensitization, compared with nonsmokers and ex-smokers (odds ratio = 3.9, 95% CI = 1.6–9.7). This result confirms results from other studies indicating that smokers have greater risks for sensitization to halogenated Pt salts than nonsmokers (Calverley et al., 1995; Venables et al., 1989).

The 100- and 1,000-fold range of concentrations within the collected stationary air and personal air samples for the high-exposure group suggests a fair amount of variance across time or space in the high-exposure work areas. The air concentrations reported by Merget et al. (2000) are lower than the lowest workplace air concentrations associated with increased prevalence of halogenated Pt salt allergic sensitization in the cross-sectional study by Baker et al. (1990), 0.4, 0.5, and 5.3 μg soluble Pt/m^3; however, the analytical methods and limits of detection used to determine the Pt concentrations in Baker et al. (1990) were not reported. The Pt air concentrations reported by Merget et al. (2000) are also lower than airborne Pt concentrations reported in the retrospective study by Linnett and Hughes (1999). However, the data from Linnet and Hughes (1999) are limited to percent of measurements above 0.5 μg soluble Pt/m^3 and percent of measurements below 0.5 μg soluble Pt/m^3 with no information on the actual exposure values of concentrations below 0.5 μg soluble Pt/m^3. The fact that Merget et al. (2000) present lower exposure concentration data than the occupational studies in Pt refineries may be related to the quantitative and qualitative differences in exposure to halogenated Pt salts between refineries and catalyst production plants (Merget et al., 2001, 2000). Pt exposure in a catalyst production plant is lower and at a more consistent level than in a refinery because the production process in a catalyst production plant is more uniform and the protective measures are intensified (Merget et al., 2001). Among the five available occupational studies that report Pt exposure concentrations and health effects, only Merget et al. (2000) is a study of workers in a catalyst production plant; the other four studies (Linnett and Hughes, 1999; Bolm-Audorff, 1992;

Baker et al., 1990; Brooks et al., 1990) are of workers in Pt refineries. Another limitation of using the data in this study to estimate dose-response relationships for chronic lifetime exposure is that the duration of exposure necessary for development of sensitization among the 13 sensitized workers in the high-exposure group was less than chronic, although somewhat variable (9 converted during year 3, with the remainder converting in years 1, 2, 4, and 5). Additional limitation of this study is that it examined a relatively narrow population: adult males healthy enough to work. Subjects in the exposed groups were predominantly (94–100%) males, whereas the no-exposure group had fewer (85%) males. Another limitation of this study is that only the concentration producing sensitization can be estimated; the exposure concentration to elicit an allergic response (which is likely much lower than that needed to produce sensitization) in sensitized individuals is not known.

4.1.2.2. *Insoluble Pt Forms*

Insoluble forms of Pt (Pt metal and PtO_2) are generally considered to be inert, thus leading to the use of alloys containing Pt metal in prostheses, including breast implants (ACGIH, 2001; Gebel, 2000; WHO, 2000, 1991). In contrast to the numerous studies evaluating adverse health effects associated with exposure to soluble Pt compounds, only one report evaluating the health effects of human exposure to inhaled insoluble Pt compounds was identified (Hunter et al., 1945). Findings of this study suggest that insoluble Pt compounds do not induce allergic sensitization. No studies have been reported on possible respiratory responses (e.g., nasal or pulmonary inflammatory responses) or other human health effects to repeated exposure to airborne particles with Pt metal or Pt oxides. Studies evaluating the allergenic potential of insoluble Pt compounds in animals were not identified (see Section 4.5.1.2, *Sensitization Studies, Insoluble Pt Forms*).

Hunter et al. (1945) reported that occupational asthma was not observed in workers primarily involved in a process involving very heavy exposure to dust of Pt metal, but that asthma and other signs of allergy were observed in workers exposed to complex halogenated Pt salts. Workers from four refineries were recruited for this study. The main process used at each refinery was reported as follows: refinery A, a wet process involving sodium chloroplatinate; refinery B, a wet process involving precipitation of ammonium chloroplatinate which was then dried; refinery C, dry ammonium chloroplatinate was "handled"; and refinery D, ammonium chloroplatinate was precipitated and then ignited to form spongy Pt. Air monitoring was conducted at multiple locations at each refinery. The duration of sample collection was reported as "usually during the whole of the operation", but specific information on the duration of sample collection (e.g., over several hours, daily work shift, or several days) was not provided; furthermore, it was not clear from the study if the same collection duration was used at all sampling locations. Total Pt in samples was determined by a colorimetric assay following acid extraction of filters; the LOD ranged from 0.5 to 10 µg Pt per sample, depending on the specific

method used (a "micro-reading technique" was used for samples with low total Pt). The ranges of total Pt concentrations in air for work areas involving Pt salts were estimated by study authors as 7–20 μg Pt/m^3 at refinery A, 1.6–50.2 μg Pt/m^3 at refinery B, 1.5–1,700 Pt μg/m^3 at refinery C, and 0.9–3.2 μg Pt/m^3 at refinery D. Total Pt air concentrations at work locations involved in sieving spongy Pt (a process that generates metallic Pt dust) were estimated at 400 μg Pt/m^3 at refinery A and 960 μg Pt/m^3 at refinery C; estimates of Pt concentrations in air of work areas conducting sieving of spongy Pt at refineries B and D were not reported.

At total of 114 workers from four refineries were enrolled in the study; 91 workers were described as having "contact with" Pt salts (Hunter et al., 1945). The remaining 23 workers were presumably exposed to metallic Pt dust during the process of sieving spongy Pt; however, the study does not include specific information regarding exposure of this group, including identification of the specific non-salt Pt compounds involved in the exposure (other than "metallic Pt dust"), the potential for these workers to be exposed to complex Pt salts during normal operations at the refinery, or history of exposure to complex Pt salts prior to the study. All participating workers were interviewed for history of nasal symptoms (sneezing, runny nose) or symptoms of asthma (chest tightness, wheeze, or shortness of breath). Chest x-rays were taken, and a physical examination was conducted. Blood samples were obtained from all study participants and were analyzed for percent hemoglobin and counts of red blood cells, total white blood cells, polymorphonuclear leukocytes, and eosinophils. SPTs to sodium chloroplatinate were conducted in 16 of 24 workers at refinery A (the remaining workers were unwilling to participate); Pt SPT were not conducted on workers at refineries B, C, or D. The report did not specific if the SPT was conducted with halogenated Pt salts (hexachloroplatinate or tetrachloroplatinate). Data on smoking history of workers was not reported. No asthma symptoms were reported by the 23 workers involved in sieving spongy Pt; no additional information on health outcomes for this group was reported. Of the 91 workers exposed to complex Pt salts, 52 workers reported symptoms of asthma and 13 workers were diagnosed with emphysema (based on chest x-ray). Dermatitis, located on exposed areas (hands, forearm, face, and neck), was observed in 13 workers. Positive SPT to sodium chloroplatinate was observed in 10 of the 16 workers participating in this test; however, the study did not report the exposure group (e.g., metallic Pt dust or complex Pt salts) for any of the 16 workers. Eosinophilia was reported in 43 of 91 workers, but exposure-related effects were not observed for the other hematological variables assessed in this study.

It is possible that repeated exposure to dusts of Pt metal or Pt oxides can lead to respiratory irritation, inflammation, or other more serious respiratory lesions, especially at concentrations that overload respiratory clearance mechanisms, as has been observed with other relatively insoluble and inert airborne materials (see Li et al., 1996; Oberdörster, 1994). For example, at high exposure levels, inhalation of insoluble nickel compounds (such as nickel oxide and nickel subsulfide) may result in decreased pulmonary clearance of these compounds, leading

to increased lung retention and the increased potential for local adverse effects (see Section 4.5.1.2 for additional information). However, no specific data on the potential respiratory irritation effects of exposure to Pt metal or Pt oxide dust in humans are available.

4.2. SUBCHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral

4.2.1.1. *Subchronic*

Few studies on the toxicity of subchronic oral exposure of laboratory animals to Pt compounds have been reported. A single 90-day oral drinking water study of 0.54 mM $PtCl_4$ in Sprague-Dawley rats (n = 4) was included as part of a series of otherwise short-term (1 and 4 weeks) exposure studies conducted by Holbrook and coworkers (Holbrook et al., 1976, 1975; Holbrook, 1976). Data on body weight or organ weight in rats exposed $PtCl_4$ for 90 days were not reported. Exposure information and estimated doses in the Holbrook studies are provided in Table 4-8 in the discussion of short-term exposure data in Section 4.4.2.1. The study only reported data on two hepatic microsomal enzymes indicative of hepatic cytochrome P450 activity and found that aniline hydroxylase activity was increased by 28% relative to control ($p < 0.05$; mean and SD not reported), but no change in aminopyrine demethylase activity was found. As discussed in Section 4.4.2, exposure to $PtCl_4$ for shorter periods (1–4 weeks) was associated with either a decrease or no change in the activities of the two hepatic microsomal enzymes reported, while this 90-day exposure was associated with an increase in one enzyme. Therefore, the conflicting and inconsistent effects of $PtCl_4$ on these endpoints are difficult to interpret and do not reflect a clearly adverse effect on the liver in the absence of additional information on potential hepatotoxicity such as histopathology or standard biochemical endpoints. Limitations in study design (e.g., a single dose tested, lack of comprehensive endpoints) do not allow for identification of other potential target organs or dose-response relationships, or comparisons of the relative potency of more-soluble (e.g., $PtCl_4$) and less-soluble Pt compounds (e.g., PtO_2).

Roshchin et al. (1984) reported that a 6-month dietary exposure of rats to Pt and palladium powder at doses of 50 mg/kg-day as well as a 6-month dietary exposure to $(NH_4)_2PtCl_6$ and a related palladium compound ($Pd[NH_3]_4Cl_2$) at doses ranging from 0.05 to 5 mg/kg-day reduced body weight gain, decreased prothrombin time, and decreased serum levels of urea and β-lipoproteins, although specific dose-response data were not reported. Increased serum concentrations of urea were also reported, and it is unclear which of the reported effects were associated with Pt compounds and which were associated with palladium compounds. Histopathological examinations of tissue were not conducted. No additional details were reported (e.g., rat strain, sex, number of animals, preparation of dosing material, magnitude of effect). Since methods and results of the Roshchin et al. (1984) study are poorly reported, it is

also unclear if treatment-related effects are specific for oral exposure or inhalation exposure, which was also evaluated in this study (see Section 4.2.2.1, *Inhalation, Subchronic*).

In summary, there are a few toxicity studies of animals following subchronic oral exposure to Pt or Pt compounds, but limitations in design (e.g., no histopathology in the studies by Holbrook and colleagues) or reporting (e.g., the report by Roshchin et al., 1984) do not allow definitive identification of health hazards.

4.2.1.2. *Chronic*

No studies on the effects of chronic oral exposure of animals to soluble or insoluble Pt compounds were identified.

4.2.2. Inhalation

4.2.2.1. *Subchronic*

Animal toxicology studies involving repeated inhalation exposure to Pt compounds are limited to a single inadequately reported study by Roshchin et al. (1984) and studies evaluating sensitization effects of inhaled halogenated Pt salts of hexachloroplatinate (Biagini et al., 1986, 1983).

Roshchin et al. (1984) reported that exposure of rats to ammonium chloroplatinate at a concentration of 18.6 mg/m^3 for 6 months (daily exposure duration not reported) appeared "to be toxic." Further clarification or descriptions of toxic effects specifically attributed to inhaled Pt exposure were not reported.

Biagini et al. (1986, 1983) exposed cynomolgus monkeys to $(NH_4)_2PtCl_6$ for 6 hours/day, 5 days/week for 12 weeks and to Na_2PtCl_6 4 hours/day, biweekly, for 12 weeks. Since the primary goal of these studies was to evaluate sensitization effects, comprehensive toxicity endpoints (e.g., gross pathology, histopathology, biochemistry, hematology, signs of toxicity) were not evaluated; additional details are described in Section 4.5.1, *Sensitization Studies*.

In summary, there are a few toxicity studies of animals subchronically exposed by inhalation to Pt compounds, but limitations in design (e.g., no histopathology in the studies by Biagini and colleagues) or reporting (e.g., the report by Roshchin et al., 1984) do not allow definitive identification of health hazards other than allergic sensitization.

4.2.2.2. *Chronic*

No studies on the effects of chronic inhalation exposure of animals to soluble or insoluble Pt compounds were identified.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

4.3.1. Oral

Studies investigating the reproductive effects of oral exposure to Pt compounds were not identified. The effect of oral exposure to Pt compounds on development and neonatal growth was reported in studies by D'Agostino et al. (1984) and Massaro et al. (1981). These studies, however, do not adequately evaluate the potential developmental effects, because dams were only exposed on a single day during gestation or lactation and comprehensive developmental endpoints (e.g., external, skeletal, or visceral malformations) were not examined. Although developmental effects were only assessed for acute oral exposure, results (exposure-related decreased body weights in offspring) indicate that Pt compounds may be toxic to the developing fetus and neonate.

D'Agostino et al. (1984; Massaro et al., 1981) administered a single gavage dose of $Pt(SO_4)_2$ (200 mg Pt/kg) to pregnant ICR Swiss mice (nine dams per dose group) on days 7 or 12 of gestation, or on day 2 postpartum. Pups from dams that received the $Pt(SO_4)_2$ dose and pups from control dams were cross-fostered. Litters from control and treated dams were culled to three males and three females prior to commencement of nursing. Culled pups from treated dams were fostered to treated and control dams; culled pups from control dams were fostered to treated and control dams. The only maternal endpoint evaluated was offspring retrieval latency (i.e., time to retrieve offspring from scattered locations to the nest), assessed during the first 2 hours of the light phase of the light cycle on day 3 postpartum. Offspring were evaluated for body weights at several intervals up to postpartum day 45, gross activity (activity field observations) on day 8 postpartum, and open field activity (e.g., ambulations, rearings, passive avoidance) and performance on a rotarod, on days 60–65 postpartum. Offspring from dams that received the oral dose of $Pt(SO_4)_2$ on gestational day 7 or 12 had significantly ($p < 0.05$) decreased body weights, compared to controls, up to postpartum day 45. Mean body weights were 1.42 ± 0.21 g at birth in the pups born to dams exposed to $Pt(SO_4)_2$ on day 12 of gestation and fostered by exposed dams, and 1.75 ± 0.21 g in pups from control dams fostered by control dams (i.e., 23% decrease in treated versus control). On day 45 postpartum, corresponding mean body weights were 25.1 ± 4.6 g in treated offspring and 29.0 ± 4.4 g in control offspring (15% decrease). The only other reported exposure-related effect was for statistically significantly ($p < 0.05$) reduced neonatal activity for treated pups on postpartum day 2 (group means and SD were not reported).

4.3.2. Inhalation

No studies on the potential reproductive/developmental effects of inhalation exposure of animals to soluble or insoluble Pt compounds were identified.

4.4. OTHER DURATION- OR ENDPOINT-SPECIFIC STUDIES AND OTHER HAZARD IDENTIFICATION ISSUES

4.4.1. Acute Exposure Studies

4.4.1.1. *Oral*

Acute lethality following oral administration to rats has been reported for several Pt compounds, as summarized in Table 4-7 (WHO, 1991; Roshchin et al., 1984; Lown et al., 1980; Holbrook, 1976; Holbrook et al., 1975). Experimental details of the acute oral toxicity studies in rats are largely unavailable, with the exception of the reports by Holbrook et al. (1975) and Roshchin et al. (1984). Holbrook et al. (1975) reported that Sprague-Dawley rats were observed for a 14-day observation period after dose administration, but did not report the range of actual doses administered or the number of rats per dose groups. Roshchin et al. (1984) reported that acute oral administration of fine dusts of Pt group metals (Pt and palladium particles of 1–5 μm diameters) at a dose of 25 mg/kg produced no deaths in rats and caused slight necrotic changes in the GI epithelium, hepatocytic granular dystrophy, and epithelial swelling in renal convoluted tubules, but did not report further experimental details for this study or for the rat LD_{50} values for $PtCl_2$, $PtCl_4$, or $(NH_4)_2PtCl_6$ in Table 4-7. The rat LD_{50} values in Table 4-7 indicate that halogenated Pt salts (e.g., salts of tetrachloroplatinic acid or hexachloroplatinic acid) generally have higher acute oral toxicity potencies than nonionic Pt compounds (e.g., PtO_2, $PtCl_2$, $Pt(SO_4)_2$) and that the water solubility of nonionic Pt compounds can influence acute oral toxicity potency (e.g., water-soluble $PtCl_4$ has a higher acute oral toxicity potency than relatively insoluble $PtCl_2$).

Table 4-7. Acute oral toxicity of Pt compounds in rats

Compound	LD_{50} (mg/kg)[a]	LD_{50} (mg Pt/kg)	Reference
PtO_2	>3,400	>2,950	Holbrook et al., 1975
	>8,000	>6,900	Holbrook, 1976
$PtCl_2$	>1,330	>975	Holbrook et al., 1975
	>2,000	>1,450	Holbrook, 1976
	3,423	2,500	WHO, 1991; Roshchin et al., 1984
$PtCl_4$	240	140	Holbrook, 1976
	276	160	WHO, 1991; Roshchin et al., 1984
	<640	<370	Holbrook et al., 1975
$Pt(SO_4)_2 (H_2O)_4$	1,010	430	Holbrook, 1976; Holbrook et al., 1975
$(NH_4)_2PtCl_4$	125–212	65–110	WHO, 1991
$(NH_4)_2PtCl_6$	195	85	WHO, 1991; Roshchin et al., 1984
H_2PtCl_6	40–50	14–19	Ward et al., 1976
Na_2PtCl_6	25–50	10–20	Johnson Matthey, 1978b (as cited in WHO, 1991)
$Na_2Pt(OH)_6$	500–2,000	285–1,140	Johnson Matthey, 1978a (as cited in WHO, 1991)
K_2PtCl_4	50–200	20–95	Johnson Matthey, 1981a, b (as cited in WHO, 1991)

[a]mg of Pt compound.

Limited acute oral toxicity data for mice support the hypothesis that halogenated Pt salts have higher acute oral toxicity potencies than nonionic Pt compounds. Lown et al. (1980) and Massaro et al. (1981) administered single gavage doses of Na_2PtCl_6 or $Pt(SO_4)_2$ to male ICR strain Swiss mice (10 animals per dose group) and reported 7-day LD_{50} values (actual doses administered were not reported). The 7-day LD_{50} value for Na_2PtCl_6 was 82.5 mg Pt/kg body weight (95% confidence limit [CL]: 72.1, 108.5). The 7-day LD_{50} value for $Pt(SO_4)_2$ was 280.5 mg Pt/kg body weight (95% CL: 237.6, 320.1). Acute LD_{50} values for Pt compounds administered by parenteral routes are generally lower than those reported for oral administration, most likely due to incomplete absorption of orally administered compounds (WHO, 1991).

The kidney appears to be a target of acute high-level exposure to insoluble Pt as displayed by the epithelial swelling in the convoluted tubules of the kidney (Roschin et al., 1984). However, as noted above, study details in Roshchin et al. (1984) do not discriminate between effects observed with exposure to Pt or palladium. Although additional data on potential renal effects of oral exposure are not available, rat deaths from acute intraperitoneal exposure to hexachloroplatinic acid (H_2PtCl_6) have been attributed to renal failure and necrotizing renal tubular lesions throughout the renal cortex (Ward et al., 1976). As part of a study of Pt anticancer agents, Ward et al. (1976) administered single intraperitoneal doses of hexachloroplatinic acid to male Fischer 344 rats (two animals per dose group) and reported 14-day LD_{50} values (actual doses administered were not reported). The LD_{50} value for hexachloroplatinic acid was estimated to be 40–50 mg/kg (approximately 14–19 mg Pt/kg;

confidence limits not reported). Severe lesions were reported in the kidney and thymus, mild lesions were reported in the peritoneal cavity, and no lesions were reported in the other organs evaluated (liver, intestine, and bone marrow). No additional information was provided on the peritoneal lesions or the thymic lesions; however, thymic lesions are consistent with stress associated thymic atrophy expected in an LD_{50} study.

No direct evidence has been reported implicating neurotoxicity of Pt compounds. The only information available on the potential neurotoxicity of Pt compounds is limited to findings of effects on gross neurobehavioral endpoints. Decreased activity, classified as "behavioral effects" by the study authors, was observed in mice exposed to acute oral $Pt(SO_4)_2$ at sublethal doses (Lown et al., 1980). In this study, male ICR Swiss mice (40 animals per dose) received a gavage dose of 144 or 213 mg Pt/kg (7-day LD_{05} and LD_{25}, respectively) as $Pt(SO_4)_2$. Open field behavior was observed at 4 hours, and 1, 3, or 7 days following dosing. Immediately following the observations, animals were sacrificed and Pt concentrations (μg/g wet weight) in tissues (blood, brain [cerebellum, cerebrum, brain stem], kidney, liver, lung, muscle, spleen, testes) were determined on 10 animals at each observation time (see Section 3.2.1 for discussion of tissue Pt measurements). Open field explorations (ambulations and rearings) were marginally depressed in mice exposed to single oral doses of approximately 144 and 213 mg Pt/kg body weight as $Pt(SO_4)_2$, with the most pronounced effects observed 4 hours after exposure. Effects did not correlate with brain levels of Pt. In another study of rats exposed to acute oral doses of $(NH_4)_2PtCl_4$, signs of toxicity included hypokinesia, piloerection, diarrhea, convulsions, labored respiration, and cyanosis (Degussa, 1989, as cited in WHO, 1991). Additional experimental details on Degussa (1989) are not available.

4.4.1.2. *Inhalation*

Little information is available regarding the acute inhalation toxicity of Pt compounds. Roshchin et al. (1984) reported that no lethality occurred in rats exposed to ammonium chloroplatinate at concentrations up to 564.6 mg/m^3 (exposure duration not reported) and chloropalladosamine at concentrations up to 678 mg/m^3. Increased serum protein ($p < 0.001$), glucose ($p < 0.001$), and cholesterol ($p < 0.001$) and decreased urea ($p < 0.002$) and lactic acid ($p < 0.002$) were observed by Roshchin et al. (1984); however, it is unclear which dose or compound the effects were associated with. Methods and results of Roshchin et al. (1984) were poorly described and further information on the degree of change for endpoints in treatment or control groups were not reported; no additional details were reported (e.g., rat strain, sex, number of animals, and preparation of dosing material).

Using a primate animal model, Biagini et al. (1985b) reported that acute inhalation exposure to Na_2PtCl_6 altered pulmonary function, producing peripheral and central airway constriction. Cynomolgus monkeys were challenged with serially increasing concentrations of aerosolized solutions of Na_2PtCl_6 (0, 0.5, 2.5, 25, and 50 mg/mL). All aerosols had a MMAD of

1.0–1.5 μm, with GSDs of 1.7–2.0. Bronchoprovocation challenges were performed for 1 minute (15 breaths), with increasing concentrations administered at 10-minute intervals. Bronchoprovocation challenge with Na_2PtCl_6 increased average pulmonary flow resistance and decreased pulmonary dynamic compliance (e.g., the extent to which the lungs can expand) in dose-dependent fashions. Increases in average pulmonary flow resistance ranged from approximately 140 to 690% and decreases in pulmonary dynamic compliance ranged from approximately 2 to 45% of control levels at concentrations of 0.5 and 50 mg/mL, respectively. Dose-dependent reductions in maximal effort flow-volume performance parameters (peak expiratory flow rate [PEFR], FEV_{05}/FVC, FEF_{50}/FVC, and FEF_{25}/FVC) were also observed, indicating both peripheral and central airway bronchoconstriction. Acute inhalation exposure to Na_2PtCl_6 did not affect respiratory rate. Companion studies evaluating the sensitization effects of acute inhalation exposure of animals to Pt compounds are reviewed in Section 4.5.1, *Sensitization Studies* (Biagini et al., 1986, 1983).

4.4.1.3. *Dermal*

Dermal irritancy of several Pt compounds was examined as part of a larger study of palladium, lead, manganese, and Pt compounds in a standard rabbit patch test for irritancy in intact and abraded skin (Campbell et al., 1975). Test material was applied to 2 × 2 cm closely clipped sites on the dorsolateral surface of each of six male albino rabbits (intact on one side and abraded on the other) weighing between 2 and 3 kg. Pt compounds included Pt dichloride ($PtCl_2$), Pt tetrachloride ($PtCl_4$), and Pt dioxide (PtO_2). The authors state that test materials in the powder state were mixed with water (0.1 g powder with 0.1 g water) and that liquid materials were applied directly in 0.1 mL quantity, but specific concentrations of the Pt compounds tested were not otherwise reported. Each application was immediately covered with gauze and secured with tape for 24 hours. After 24 hours, the covering was removed, test sites were washed and dried, evaluated, and then valuated again following an additional 48 hours. A four-point rating scale (0–1 nonirritant and nontoxic for cellular components of skin; 1–1.9 mild irritant and mild cellular toxin; 2–4 irritant and cellular toxin) was employed and means reported for each of the Pt compounds were as follows: 0 intact and 0 abraded for PtO_2; 0.2 intact and 0.6 abraded for $PtCl_2$; and 1.8 intact and 2.6 abraded for $PtCl_4$. Under the test conditions, the two non-soluble Pt compounds were rated nonirritants and $PtCl_4$, the only soluble compound tested, was rated a mild irritant with evidence of cellular toxicity in abraded skin.

4.4.2. Short-term Exposure Studies

4.4.2.1. *Oral*

Few studies on the toxicity of short-term oral exposure of laboratory animals to Pt compounds have been reported. Short-term oral exposure studies are available for $PtCl_4$, $Pt(SO_4)_2$, $(NH_4)_2PtCl_6$, and PtO_2 (Reichlmayr-Lais et al., 1992; Roshchin et al., 1984; Lown et

al., 1980; Holbrook, 1976; Holbrook et al., 1976, 1975). Results of available studies identify the kidney as a target organ for halogenated Pt salts and Pt compounds; however, available data are inadequate to fully characterize nephrotoxic effects or to define the exposure-response relationship for nephrotoxicity. Furthermore, available studies do not evaluate comprehensive toxicity endpoints, such as histopathology or standard biochemical and hematological endpoints, or provide dose-response data.

A series of experiments conducted by Holbrook and coworkers (Holbrook et al., 1976, 1975; Holbrook, 1976) evaluated the effects of repeated exposure of male Sprague-Dawley rats to Pt compounds in drinking water or diet on body weight gain, organ weights (liver, kidney, spleen, heart, and testes), and activities of two hepatic microsomal enzymes (aniline hydroxylase, aminopyrine demethylase) indicative of hepatic cytochrome P450 activity. Histopathology effects and effects on standard biochemical or hematological endpoints were not evaluated in these studies. Exposure information and estimated doses in the Holbrook studies (Holbrook et al., 1976, 1975; Holbrook, 1976) are provided in Table 4-8. Daily dose estimates (mg/kg-day) were not reported in these studies. Because data on body weight and food and water consumption were incompletely reported, the estimated doses shown in Table 4-8 are based on U.S. EPA (1988) reference values for water and food consumption in male Sprague-Dawley rats.

Table 4-8. Exposures, estimated doses, and effects in Sprague-Dawley rats exposed to Pt compounds in drinking water or diet

Compound	Medium	Exposure duration (days)	N	Exposure concentration[a]		Estimated dose[b] (mg Pt/kg-day)	Effects		
				(mmol/L or kg)	(mg Pt/L or kg)		Body weight gain	Change in organ weight[c]	Microsomal enzyme activity[d]
$PtCl_4$	Water	8–9	12	1.63	318	44.1	No change	No change	No change/ Decreased[e]
$PtCl_4$	Water	8–9	4	2.45	495	68.6	Decreased	Not reported	No change
$PtCl_4$	Water	29–31	8	0.54	105	14.6	No change	No change	No change
$PtCl_4$	Water	29–31	12	1.63	318	44.1	Decreased (1^{st} wk only)	Increased (kidney only)	No change
$PtCl_4$	Water	90–91	4	0.54	105	14.6	Not reported	Not reported	Increased[f]
$Pt(SO_4)_2$	Water	8–9	8	1.63	318	44.1	Decreased	No change	Decreased[g]
$PtCl_4$	Food	29–31	12	5.90	1,151	99.2	No change	Not reported	No change
$PtCl_4$	Food	29–31	4	13.2	2,575	222	No change	Not reported	Increased[h]
$Pt(SO_4)_2$	Food	29–31	4	5.90	1,151	99.2	No change	Not reported	No change
PtO_2	Food	29–31	4	29.8	5,813	501	No change	Not reported	No change

[a]Exposure concentration, mmol/L or mg/L drinking water; mmol/kg or mg/kg food
[b]mg/kg-day = mg/L drinking water × 0.037 L water/day/0.267 kg body weight (for subchronic exposure, male Sprague-Dawley rat; U.S. EPA, 1988)
mg/kg-day = mg/kg food × 0.023 kg food/day/0.267 kg body weight (for subchronic exposure, male Sprague-Dawley rat; U.S. EPA, 1988)
[c]Organ weight taken of liver, kidney, spleen, heart, and testes.
[d]Aniline hydroxylase and aminopyrine demethylase activities
[e]Holbrook et al. (1975) reported that activity of aniline hydroxylase was decreased by 21% and that no effects on aminopyrine demethylase activity were observed. However, a later report of the same study (Holbrook et al., 1976) reported no change in either enzyme following exposure to 1.63 mM $PtCl_4$ for 8–9 days.
[f]Aniline hydroxylase activity was increased ($p < 0.05$; mean and SD not reported) by 28%, compared with control, but no change in aminopyrine demethylase activity was found.
[g]Aniline hydroxylase activity was decreased ($p < 0.05$; mean and SD were not reported) by 21%, compared with control, but no change in aminopyrine demethylase activity was found.
[h]Aminopyrine demethylase activity was increased ($p < 0.1$; mean and SD were not reported) by 22%, compared with control, but no change in aniline hydroxylase activity was found.

Sources: Holbrook (1976); Holbrook et al. (1976, 1975).

Results of the drinking water studies are summarized in Table 4-8. No effect on body weight gain was observed for rats exposed to 1.63 mM $PtCl_4$ for 8–9 days, or 0.54 mM $PtCl_4$ for 29–31 days. Body weight gain was reduced by approximately 25% in rats exposed to 2.45 mM $PtCl_4$ in drinking water for 8–9 days (SD and statistical significance were not reported). Exposure for 29–31 days to 1.63 mM $PtCl_4$ resulted in a 20% reduction in body weight gain during the first week of exposure only; decreases in weight gain were accompanied by a 20% reduction in food and water consumption (SD or statistical significance not reported). Body weight gain was decreased by 14% (SD or statistical significance not reported) in rats exposed to 1.63 mM $Pt(SO_4)_2$ for 8–9 days. Data on body weight gain in rats exposed to 0.54 mM $PtCl_4$ for 90–91 days were not reported. Exposure to 0.54 mM $PtCl_4$ in drinking water for 29–31 days did not affect weights of any of the five organs investigated (liver, kidney, spleen, heart, and testes); organ weight data for rats exposed to 0.54 mM $PtCl_4$ for 90–91 days (see Section 4.2.1.1 for complete discussion of the subchronic exposure portion of this study) or 2.45 mM $PtCl_4$ for 8–9 days were not reported. No changes in organ weights were observed in rats exposed to 1.63 mM rat $PtCl_4$ or 1.63 mM $Pt(SO_4)_2$ for 8–9 days. However, exposure to 1.63 mM rat $PtCl_4$ for 29-31 days resulted in a slight increase in kidney weight as a percentage of body weight, from 0.85% in controls to 0.92% in the $PtCl_4$ group (8% increase; $p < 0.05$; SD not reported) (Holbrook et al., 1975), but no changes in weights of other organs were observed. Reported results for activities of aniline hydroxylase and aminopyrine demethylase provide mixed evidence for induction of hepatic cytochrome P450 with 90–91 days of exposure to 0.54 mM $PtCl_4$: aniline hydroxylase activity was increased by 28% compared with control ($p < 0.05$), but aminopyrine demethylase activity was unchanged (Table 4-8). With shorter durations of exposure (8–9 or 29–31 days) to $PtCl_4$ or $Pt(SO_4)_2$, no consistent evidence for exposure-related changes in these hepatic enzymes was found (see Table 4-8). In the absence of histological examinations or other endpoints indicative of liver damage, the evidence for $PtCl_4$ induction of hepatic cytochrome P450 is not judged to be an adverse effect on the liver.

Holbrook et al. (1976, 1975; Holbrook, 1976) also exposed Sprague-Dawley rats to $PtCl_4$, $Pt(SO4)_2$, or PtO_2 in the diet for 29–31 days (exposures, estimated doses, and results are summarized in Table 4-8). No discernable effects on body weight were found for any of the exposed groups of rats. No data on the effect of dietary exposure on organ weights were reported for any group. Exposure to $PtCl_4$ in the diet (13.2 mmol/kg diet or 222 mg Pt/kg body weight-day) was associated with a 22% increase in hepatic microsomal aminopyrine demethylase activity ($p < 0.10$, SD not reported), but no other changes in microsomal enzyme activities were observed for the other groups exposed to Pt compounds in the diet.

As further evidence for an effect of $PtCl_4$ on hepatic cytochrome P450 activity, Holbrook et al. (1976) reported a dose-dependent increase in hexobarbital sleeping time in male Sprague-Dawley rats (number of animals per dose group were not reported) following two daily intraperitoneal doses of $PtCl_4$ ranging from 14 to 56 μmol Pt/kg-day (2.73–10.9 mg Pt/kg-day);

the increase was 51 ± 15 (SD)% ($p < 0.05$%) at the highest dose (22.0 mg Pt/kg-day). The increase in hexobarbital sleeping time is indicative of a decrease in metabolism of hexobarbital by cytochrome P450.

In summary, the Holbrook (1976) and Holbrook et al. (1975) studies provide suggestive evidence for the possibility of kidney toxicity in rats exposed to1.63 mM $PtCl_4$ in drinking water (≈44.1 mg Pt/kg-day) for 29 days (i.e., 8% increase in relative kidney weight), but no histopathological examinations of kidney or any other organs were conducted. The inconsistent effects (i.e., increase, decrease, and no change) reported in these studies on activities of the hepatic microsomal enzymes, aniline hydroxylase and aminopyrine demethylase, are difficult to interpret and do not reflect a clearly adverse effect on the liver. Limitations in study design (e.g., few doses tested, lack of comprehensive endpoints) do not allow for identification of other potential target organs or dose-response relationships, or comparisons of the relative potency of more-soluble (e.g., $PtCl_4$, $Pt[SO_4]_2$) and less-soluble Pt compounds (e.g., PtO_2).

Reichlmayr-Lais et al. (1992) exposed Sprague-Dawley rats (nine animals per dose group) for 4 weeks to $PtCl_2$ or $PtCl_4$ in diet at concentrations of 0, 0.01, 0.05, 0.1, 0.5, 1, 5, 10, and 50 mg Pt per kg diet. Using an average body weight (based on an average initial body weight of 35 g and the average total body weight gain over 4 weeks for each treatment group) and the total Pt intake reported for the 4-week exposure period for each treatment group, daily Pt doses were estimated at 0.001, 0.006, 0.01, 0.06, 0.1, 0.5, 1, and 6 mg Pt/kg-day for the 0.01, 0.05, 0.1, 0.5, 1, 5, 10, and 50 mg Pt groups, respectively, for both $PtCl_2$ and $PtCl_4$ groups. The following assessments were made on animals at the conclusion of exposure: food consumption, body weight, hematology (i.e., erythrocyte count, mean corpuscular volume [MCV], hematocrit, hemoglobin), and plasma creatinine concentration. Pt concentrations in tissues (adipose, brain, carcass, femur, heart, kidney, liver, muscle, plasma, spleen, testes) were measured by AAS (see Section 3.2.1 for summary of tissue Pt data). Body weight gain and food intake were unaffected by dietary exposure to $PtCl_2$ and $PtCl_4$. No treatment-related effects on hematological parameters (erythrocytes count, hematocrit, MCV, and hemoglobin) were observed in any $PtCl_2$ group. A trend ($p < 0.06$) was observed in rats treated with $PtCl_4$ for decreased erythrocytes number and hematocrit. Approximate maximum percentage decreases observed in the highest dose $PtCl_4$ group were 13% for mean erythrocyte count (5.11 ± 0.50 [SD] × 10^6/μL versus 5.88 ± 0.55 × 10^6/μL in the control group) and 13% for mean hematocrit (29.1 ± 3.3 versus 32.9 ± 3.1 in the control group). Plasma creatinine was also significantly ($p < 0.05$) increased in the 6 mg $PtCl_4$ group (1.45 ± 0.19 mg/dL versus 0.7 ± 0.47 [SD] mg/dL in control), indicating altered renal function. No other measure of renal function or additional information on potential histopathological changes to the kidney or other organs was reported. Decreased erythrocyte count and increased creatinine clearance indicate that the 4-week dietary exposure to $PtCl_4$, but not $PtCl_2$, may adversely affect the hematopoietic system and the kidney at the doses tested.

Reduced activity (marginally reduced rearing and exploratory activity) were observed in rats exposed to repeated oral dose of 109 mg Pt/kg body weight as $Pt(SO_4)_2$ (1–10 doses over 30 days) (Lown et al., 1980).

In summary, short-term oral studies (Reichlmayr-Lais et al., 1992; Roshchin et al., 1984; Holbrook, 1976; Holbrook et al., 1976, 1975) provide evidence for the kidney as a possible target of toxicity of soluble Pt compounds in rats (i.e., $PtCl_4$, $Pt[SO_4]_2$), but are limited in scope and did not include histopathological examinations. Evidence in support of this conclusion include observations of an 8% increase in relative kidney weight in rats exposed to 1.63 mM $PtCl_4$ in drinking water for 29 days (≈44.1 mg Pt/kg-day; Holbrook et al., 1975) and an increase in plasma creatinine concentration in rats exposed to 50 mg Pt per kg diet as $PtCl_4$ in diet for 4 weeks (≈6 mg Pt/kg-day; Reichlmayr-Lais et al., 1992). The studies provide less convincing evidence that the liver is a potential toxicity target of repeated oral exposure to soluble Pt compounds. Changes in activities of the hepatic microsomal enzymes (e.g., aniline hydroxylase and aminopyrine demethylase) have also been observed in rats exposed to $PtCl_4$ or $Pt(SO_4)_2$ in drinking water at concentrations of 1.63 or 2.45 mM (≈44.1 or 68.6 mg Pt/kg-day) or to $PtCl_4$ in food at a concentration of 13.2 mmol/kg food (≈222 mg Pt/kg-day; Holbrook et al., 1976, 1975); however, the observed changes have not been consistent in direction (i.e., increase or decrease in enzyme activity) or repeatable across oral exposure studies. The observation that intraperitoneal dosing with $PtCl_4$ prolonged hexobarbital sleeping time in rats provides further evidence that $PtCl_4$ may alter in vivo cytochrome P450 activity (Holbrook et al., 1976), but the toxicological significance of these liver effects (i.e., their connection to a mode of action for toxicity in the liver or other tissues) in association with oral exposures to $PtCl_4$ or $Pt(SO_4)_2$ cannot be determined from the available information. One of the studies reported a trend for decreased erythrocyte number and hematocrit in rats treated exposed to $PtCl_4$ in the diet for 4 weeks, with decreases of approximately 13% for erythrocyte count and hematocrit in rats exposed to 50 mg $PtCl_4$ per kg diet (≈6 mg Pt/kg-day; Reichlmayr-Lais et al., 1992). These observations suggest that, in addition to kidney, the liver and blood may be potential target tissues for oral exposures to soluble Pt compounds. However, limitations in study design (e.g., few doses tested, lack of comprehensive assessment of endpoints, including histopathology of potential target tissues) do not allow for more definitive identification of target organs, characterization of dose-response relationships, or comparisons of relative potency of more-soluble (e.g., $PtCl_4$, $Pt[SO_4]_2$) and less-soluble Pt compounds (e.g., PtO_2).

4.4.2.2. *Inhalation*

No studies on the effects of short-term inhalation exposure of animals to soluble or insoluble Pt compounds were identified.

4.4.3. Drug Studies

Drugs containing Pt are used frequently to treat cancers of the testes, ovaries, breast, lung, head, and neck (Screnci and McKeage, 1999; WHO, 1991; IARC 1987, 1981). The Pt anticancer drugs currently approved for clinical use are cisplatin (*cis*-dichlorodiammine Pt), carboplatin (diamminecyclobutane-dicarboxylato-Pt), and oxaliplatin (*cis*-1,2-cyclohexane-diamine-N,N'-oxalato-2-O,O'-Pt), although a large number of carboplatin analogues have been developed and tested to various degrees in clinical trials (Sanderson et al., 1996). The extensive clinical experience with Pt anticancer drugs provides a large body of information regarding adverse effects of those Pt compounds in humans at high doses and generally after acute or short-term parenteral exposure. Although no studies are available examining possible associations between inhalation exposure to Pt anticancer drugs and specific adverse health effects, information on adverse effects associated with parenteral and oral exposure to Pt anticancer drugs in human subjects indicates the potential for a range of Pt-induced adverse health effects. Adverse effect profiles of the Pt anticancer drugs vary with specific compound (as discussed in Section 4.4.3.2 and summarized in Table 4-10). Predominant toxic effects of the three main parenteral forms of Pt anticancer drugs include nephrotoxicity (cisplatin), ototoxicity (cisplatin), neurotoxicity (cisplatin and oxaliplatin), myelotoxicity (carboplatin), gastrointestinal toxicity (all three of the main parenteral forms), and allergic sensitization (all three of the main parenteral forms) (Hartmann and Lipp, 2003). Treatment of humans and animals with the newer, experimental oral Pt anticancer drug JM216 has been associated with myelosuppression and gastrointestinal toxicity, but not ototoxicity. However, due to the limited clinical experience with these drugs, the nephrotoxic, neurotoxic, and sensitization potential of JM216 or the other experimental oral drugs has not been established (Screnci and McKeage, 1999; Sessa et al., 1998; McKeage, 1995). The precise mechanism of anticancer activity of the Pt anticancer drugs has not been fully elucidated, although the mechanism appears to involve the inability of tumor cells to repair special intra-strand DNA cross-links that are formed by cisplatin (Hartmann and Lipp, 2003; Lawley and Phillips, 1996; WHO, 1991). Anticancer activity is highly dependent upon chemical structure and spatial orientation, as indicated by the lack of anticancer activity by the trans isomer of cisplatin (Hartmann and Lipp, 2003; Lawley and Phillips, 1996; Arany and Safirstein, 2003; WHO, 1991). As described below, although Pt anticancer drugs share similar structures, they differ in pharmacokinetic and toxicity profiles (Hartmann and Lipp, 2003).

4.4.3.1. *Pharmacokinetics of Pt Anticancer Drugs*

Treatment with parenteral Pt anticancer drugs typically involves a course of intravenous or intraperitoneal injections, most commonly administered by intravenous infusion lasting from minutes to 24 hours (Calvert et al., 1993). As shown in Table 4-9, the pharmacokinetic properties of Pt anticancer drugs vary with specific compound. Pt anticancer drugs vary widely with respect to binding to plasma proteins; >90% of administered cisplatin is irreversibly bound

to plasma proteins, compared to approximately 24–50% for carboplatin and 85% for oxaliplatin (Hartmann and Lipp, 2003; Chabner et al., 2001). The distribution of the cisplatin, carboplatin, oxaliplatin, and JM40 (an experimental oral Pt anticancer drug) appears to be biphasic (e.g., an initial phase, α, which reflects distribution from the blood to tissues with high perfusion, and a second phase, β, which reflects the time required for tissue concentrations to reach equilibrium with the blood). Cisplatin, carboplatin, and JM40 are rapidly distributed within the body, with initial distribution half-lives of 0.22, 0.37, and 0.2 hours, respectively; whereas the initial distribution of oxaliplatin is much slower, showing an initial distribution half-life of 7.3 hours (Chabner et al., 2001; Graham et al., 2000; Calvert et al., 1993). Pt anticancer drugs are widely distributed in the body. At steady state, oxaliplatin has the largest volume of distribution (295–812 L), followed by carboplatin (176 L), JM40 (62 L), and cisplatin (52 L) (Graham et al., 2000; Calvert et al., 1993). Similar tissue distribution of Pt has been reported for cisplatin and carboplatin, with the highest concentration of Pt observed in the kidney for cisplatin and carboplatin (Chabner et al., 2001; Tinker et al., 1990). For cisplatin, Pt appears to concentrate in the kidney in areas of functional and histological damage (Arany and Safirstein, 2003; McKeage, 1995). Penetration into the central nervous system is poor for all Pt anticancer drugs (Chabner et al., 2001). Cisplatin has been reported to cross the placenta in humans and rats (Hartmann and Lipp, 2003; Pascual et al., 2001).

Table 4-9. Summary of pharmacokinetics properties for Pt anticancer drugs

Property	Cisplatin	Carboplatin	Oxaliplatin	JM40
Route of administration	Parenteral	Parenteral	Parenteral	Oral
Binding to plasma proteins	>90%[a,b]	24–50%[b]	80–87%[a,b,c]	NA
Distribution half-life α	0.22 hr[c]	0.37 hr[c]	7.3 hr[c]	0.2 hr[d]
Distribution half-life β	0.72 hr[c]	1.93 hr[c]	239 hr[c]	1 hr[d]
Initial volume of distribution	10L[d]	10 L[d]	NA	12 L[d]
Volume of distribution at steady-state	52 L[d]	176 L[d]	295–812 L[c,d]	62 L[d]
Tissue distribution	Kidney, liver, intestine, testes[a]	Kidney, liver, lung, spleen, testes[e]	NA	NA[f]
Crosses placenta	Yes[b,g]	NA	NA	NA
CNS penetration	Poor[a]	Poor[a]	Poor[a]	NA[f]
Primary elimination routes	Renal excretion (GFR and tubular secretion) and metabolism[a,b]	Renal excretion (GFR)[b,d]	Renal excretion (GFR) and metabolism[a]	Renal excretion and metabolism[a,h]
Total body clearance	0.35 L/hr[d]	1.38 L/hr[d]	0.96 L/hr[c]	0.54 L/hr[d]
Terminal half-life	5.4 d[c,d,i]	5.8 d[c,d,i]	10.5–26 d[a,b,c]	4.1 d[d]

[a]Chabner et al. (2001).
[b]Hartmann and Lipp (2003).
[c]Graham et al. (2000).
[d]Calvert et al. (1993).
[e]Tinker et al. (1990).
[f]Data on the tissue distribution of the experimental oral drug, JM216, in mice (following oral administration) show distribution to the kidney, liver, lung, spleen, and brain (demonstrating poor central nervous system penetration), with the highest tissue concentration in the liver. Distribution to the testes was not examined (Bates et al., 1996).
[g]Pascual et al. (2001).
[h]Information on the specific mechanism of renal excretion of JM40 was not identified in the retrieved literature.
[i]McKeage (1995).

GFR = glomerular filtration rate; NA = information not available in the retrieved literature

Physiologically based pharmacokinetic (PBPK) models of the Pt anticancer agents have not been reported. Pharmacokinetics of various Pt anticancer agents (e.g., cisplatin) have been characterized with empirical models. The empirical models have been derived by fitting mathematical expressions (e.g., first-order rate equations) to data on plasma concentrations of Pt or urinary excretion of Pt in humans following single or multiple doses of Pt compounds. The models were derived to estimate specific pharmacokinetic parameters relevant to prediction of dosing regimes needed to achieve therapeutic levels of the agents (e.g., distribution and elimination half-times, volumes of distribution, clearances, area under plasma concentration-time profiles, binding constants). The models do not identify or parameterize specific physiological compartments (e.g., tissues). Examples of empirical models for several anti-cancer agents are presented in Table 4-9.

Metabolism and binding of Pt anticancer drugs appears to relate to the reactivity of the leaving groups. Pt anti-cancer agents (e.g., derivatives of cisplatin) include a variety of diamine-Pt (II) or Pt(IV) compounds having the general structures *cis*$[PtX_2(NHR_2)_2]$ or *cis*$[PtX_4(NHR_2)_2]$, respectively, where R is an organic moiety and X is a leaving group (Cl in cisplatin). These compounds undergo a variety of nonenzymatic ligand exchange reactions with amino acids, proteins and nucleic acid bases (Reedijk, 2003; Calvert et al., 1993). The reactions occur by hydrolysis of the non-amine leaving group, which yields reactive intermediates (e.g., $[PtCl(H_2O)(NH_3)_2]^+$ from cisplatin) leading to the formation of Pt-adducts (Reedijk, 2003). Reactivity is related to stability of the leaving group relative to that of the donor group ($NO_3^- < SO_4^{2-} < Cl^-$; Calvert et al., 1993). Relatively high stability of S-donor ligands results in formation of Pt-sulfur complexes with sulfur amino acids (e.g., cysteine, methionine) in proteins and peptides (e.g., glutathione). Formation of Pt-DNA adducts (e.g., Pt-guanine) may involve migration of Pt from a sulfur ligand intermediate (Reedijk, 2003). The affinity of Pt for sulfur is the main pharmacologic rationale for the use of thiol agents (e.g., diethyldithiocarbamate, thiosulphate) for mitigating toxicity of cisplatin and related anticancer agents (McKeage, 1995; Calvert et al., 1993). Pt(IV) anticancer agents (e.g., iprorplatin, tetraplatin) can undergo intracellular reduction to Pt(II) species (Calvert et al., 1993). Reduction may influence reactivity of diamine-Pt compounds with DNA (Reedijk, 2003; Calvert et al., 1993). The exact mechanisms for the reduction have not been elucidated; however, redox potential of diamine-Pt complexes is influenced by substituents on the amine groups (Reedijk, 2003).

Pt anticancer drugs are eliminated through a combination of metabolism and renal excretion, with most metabolites formed through non-enzymatic reactions (Calvert et al., 1993). Renal excretion is the predominant excretory route, with a high percentage of administered dose eliminated in the urine (Chabner et al., 2001; Graham et al., 2000; Calvert et al., 1993). For cisplatin, approximately 43% of the administered dose is recovered in the urine (compound measured in urine was not specified) within 5 days (Chabner et al., 2001) and approximately 65% of carboplatin is excreted unchanged in the urine within 48 hours of administration of a single intravenous dose (Calvert et al., 1993). Renal excretion of cisplatin is by glomerular filtration and active proximal tubular secretion by organic anion and cation transport mechanisms (Arany and Safirstein, 2003; Hartmann and Lipp, 2003; McKeage, 1995). However, since the renal elimination of carboplatin and oxaliplatin has been reported to closely approximate the glomerular filtration rate, it appears that carboplatin and oxaliplatin do not undergo significant tubular reabsorption or secretion (Hartmann and Lipp, 2003; Graham et al., 2000; Calvert et al., 1993). As discussed in Section 4.4.3.3, the higher nephrotoxic potency of cisplatin, compared to carboplatin and oxaliplatin may, in part, be related to its renal tubular secretion. Cisplatin, oxaliplatin, and JM40 also are eliminated by metabolism, whereas metabolism does not significantly contribute to the elimination of carboplatin. Pt has been reported to be excreted in breast milk following treatment with cisplatin (De Vries et al., 1989). The terminal elimination

half-life for cisplatin, carboplatin, and JM40 are 5.4, 5.8, and 4.1 days, respectively (Graham et al., 2000; McKeage et al., 1995; Calvert et al., 1993). Compared to cisplatin and carboplatin, oxaliplatin is eliminated much more slowly, with a terminal elimination half-life ranging from 10.5 to 26 days (Hartmann and Lipp, 2003; Chabner et al., 2001; Graham et al., 2000).

Studies conducted on the anti-cancer drugs, cisplatin and carboplatin, provide evidence for transdermal absorption of these compounds. Dermal application of carboplatin dissolved in dimethylsulfoxide (DMSO) or cisplatin dissolved in dimethylformamide (DMF) delay the onset of adjuvant arthritis in rats induced by subcutaneous injections of an arthritogens (Fairlie et al., 1991). These observations suggest that these Pt compounds and/or complexes with the solvents were absorbed transdermally.

In summary, the pharmacokinetics of Pt anticancer drugs are variable and depend on the specific chemical in question. The distribution of cisplatin, carboplatin, and JM40 is more rapid than for oxaliplatin. Although all Pt anticancer drugs undergo wide distribution, the volume of distribution of oxaliplatin is much larger than that of cisplatin, carboplatin, or JM40. The highest organ concentration of Pt is observed in the kidney for cisplatin and carboplatin. Cisplatin, oxaliplatin, and JM40 are eliminated through metabolism and renal excretion, whereas carboplatin is primarily eliminated by renal excretion. The mechanisms of renal excretion for cisplatin are glomerular filtration and tubular secretion, whereas carboplatin and oxaliplatin are primarily excreted via glomerular filtration. The renal tubular secretion of cisplatin may play an important role in the higher relative nephrotoxicity of cisplatin compared to other Pt anticancer drugs (see Section 4.4.3.2 for detailed discussion of cisplatin-induced nephrotoxicity). Oxaliplatin is eliminated from the body much more slowly than cisplatin, carboplatin, or JM40.

4.4.3.2. *Anticancer and Adverse Effects of Pt Anticancer Drugs*

Anticancer chemotherapeutic agents, such as the Pt anticancer drugs, are typically administered at maximum tolerated doses with respect to adverse effects; as such, serious toxicity is commonly associated with administration of therapeutic doses (Ishibashi et al., 2003). Although the Pt anticancer drugs are structurally similar, toxicity profiles differ. Cisplatin is primarily associated with nephrotoxicity, neurotoxicity, and ototoxicity, whereas myelotoxicity is predominant for carboplatin, and neurotoxicity is predominant for oxaliplatin (Arany and Safirstein, 2003; Hartmann and Lipp, 2003; Links and Lewis, 1999; Screnci and McKeage, 1999; Cersosimo, 1993). For example, a 97% prevalence of peripheral neuropathy (paraestheias, dysaetheisa, and sensory ataxia) was reported in a clinical trial of 107 patients with colorectal cancer treated with oxaliplatin, whereas a 47% prevalence of peripheral neuropathy (paraesthesia and sensory ataxia) was reported in a clinical trial of cisplatin in 292 ovarian cancer patients and a 6% prevalence was found in a trial of carboplatin in 428 patients with various tumor types (Screnci and McKeage, 1999). In general, Pt anticancer drugs are not classified as hepatotoxic drugs, although mild, reversible increases in liver function tests have been reported (Hartmann

and Lipp, 2003). The major toxicities associated with Pt anticancer drugs in humans have been well-described.

Information on the characteristics of cisplatin-induced nephrotoxicity has been summarized in reviews and is based on data from humans and experimental animals (Hartmann and Lipp, 2003; McKeage, 1995; Calvert et al., 1993). Cisplatin-induced nephrotoxicity is characterized by degenerative lesions of the proximal and distal convoluted tubules of the corticomedullary junction and the outer stripe of the medulla (Hartmann and Lipp, 2003; McKeage, 1995). Acute histopathological changes include cellular necrosis, flattening of the epithelium, hydropic degeneration, nuclear hyperchromasia, and congestion of the vasa recta. With chronic damage, cellular atrophy, tubular dilatation, nuclear atypia, and interstitial inflammation are observed (McKeage, 1995). The initiating event is a proximal tubular lesion, which results in decreased proximal tubular reabsorption of water and sodium, followed by alterations in distal tubular reabsorption, renal vascular resistance, renal blood flow, and glomerular filtration rate (GFR) (McKeage, 1995). Hypomagnesemia and potassium and calcium wasting may result from prolonged renal damage (McKeage, 1995). The most sensitive indicators of cisplatin-induced nephrotoxicity are changes in creatinine clearance, and urinary activities of alanine aminopeptidase and N-acetyl-β-D-glucosamidase (Hartmann and Lipp, 2003). Reduced renal toxicity of cisplatin through a combination of NaCl infusion and mannitol-induced water diuresis is thought to be due to suppression of the formation of "aquated" species in the renal tubule (Calvert et al., 1993). Tubular epithelial damage may be related to the renal accumulation, urinary excretion, and renal tubular secretion of cisplatin (McKeage, 1995). Differences in renal handling of carboplatin and oxaliplatin (e.g., compounds do not undergo tubular secretion) may contribute to the reduced nephrotoxicity of these agents relative to cisplatin (McKeage, 1995); severe nephrotoxicity is uncommon in patients treated with carboplatin and only rarely observed for oxaliplatin (Hartmann and Lipp, 2003). It has also been proposed that the reduced nephrotoxicity of carboplatin and oxaliplatin may be due to reduced reactivity of the leaving group (e.g., NH_3, RNH_2; not easily displaced by a nucleophile) (Hartmann and Lipp, 2003; Calvert et al., 1993).

Several reports indicate that hypersensitivity reactions to Pt anticancer drugs occur (see review by Shepherd, 2003). Symptoms of hypersensitivity reactions include respiratory symptoms (wheeze and dyspnea), GI discomfort (abdominal cramps and diarrhea), and rashes (pruritus, urticaria, facial erythema, and edema) (Hartmann and Lipp, 2003). In sensitive patients, hypersensitivity reactions are reported to occur after the administration of multiple intravenous courses of Pt anticancer drugs (Hartmann and Lipp, 2003; Markman et al., 2003). Hypersensitivity reactions to carboplatin, typical of a Type I, IgE-mediated mechanism and ranging in severity from mild to severe, were reported in 16% of the 194 patients treated intravenously with carboplatin for ovarian cancer in a Greek hospital over a 10-year period (Polyzos et al., 2001). Also, in a clinical trial study of cisplatin in which 30 patients were

administered a dose of 75 mg/m^2, 1 had to be removed from the study for hypersensitivity, and 4 were removed for renal toxicity (Sabbatini et al., 2004). Intravenous oxaliplatin induced hypersensitivity reactions in 17 of 124 patients (13%), with reactions observed after 2–17 administrations (Brandi et al., 2003). Hypersensitivity reactions to oxaliplatin have also been reported in case studies (Bhargava et al., 2004; Thomas et al., 2003). Based on the overall clinical experience with Pt anticancer drugs, the incidence of hypersensitivity reactions has been estimated as 5% for cisplatin, 2–9% for carboplatin, and <1% for oxaliplatin (Lim et al., 2004).

Cross-sensitivity is possible among the Pt anticancer drugs (Hartmann and Lipp, 2003). Results of a study by Markman et al. (2003) suggest that patients with a prior history of systemic hypersensitivity reactions to medications or environmental exposures may be predisposed to allergic reaction to Pt anticancer drugs. Since hypersensitivity from therapeutic treatment with Pt anticancer drugs prevents further use in patients with severe reactions, desensitization protocols have been developed in order for patients to continue with Pt anticancer drug therapy (Bhargava et al., 2004).

Peripheral neurotoxicity is one of the major adverse effects associated with cisplatin and oxaliplatin, occurring in approximately 50% of patients treated with cisplatin and nearly all patients treated with oxaliplatin (Screnci and McKeage, 1999). Neurotoxicity associated with administration of carboplatin is generally mild and occurs in approximately 5% of patients (Screnci and McKeage, 1999). Symptoms of neurotoxicity include numbness and tingling, paraesthesia of the upper and lower extremities, reduced deep-tendon reflexes, and leg weakness with disturbances in gait (Hartmann and Lipp, 2003). Neurotoxicity is characterized by slowing of sensory nerve conduction, prolongation or disappearance of sensory nerve latency, absence or reduction in sensory action potential, and normal motor conduction (McKeage, 1995). Histopathologically, changes include degeneration and loss of medium- to large-sized myelinated fibers, axonal degeneration, and degeneration of myelin sheaths (McKeage, 1995). Cellular changes in the dorsal route ganglia included reduced cell size, increased multinucleolization, and hypertrophy of satellite cells (McKeage, 1995). The underlying mechanism for peripheral neuropathy of Pt anticancer drugs has not been identified (Hartmann and Lipp, 2003; McKeage, 1995).

Administration of therapeutic doses of cisplatin is also associated with ototoxicity, characterized by tinnitus and bilateral high-frequency hearing loss (Hartmann and Lipp, 2003; Chabner et al., 2001; McKeage, 1995). The incidence of cisplatin-induced ototoxicity ranges from 11 to 91% (McKeage, 1995). At therapeutic doses, carboplatin rarely causes ototoxicity, with a reported incidence of 1.1% (Hartmann and Lipp, 2003). Oxaliplatin has not been reported to induce ototoxicity (Hartmann and Lipp, 2003). Cisplatin-induced histological effects are primarily cochlear damage with hair cell loss, although some studies suggest nerve damage and degenerative changes to the spiral ganglia and cochlear nerve (McKeage, 1995).

In addition to adverse effects associated with therapeutic use of Pt anticancer drugs, cisplatin has been classified by the International Agency for Research on Cancer (IARC) (1987) in cancer Group 2A, *probably carcinogenic to humans*, based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (increased incidence of tumors in rats and mice following multiple intraperitoneal injections). Although no cancer bioassays are available for other Pt anticancer drugs, positive results from genotoxicity studies suggest possible carcinogenic activity. Based on the mechanism of anticancer activity (e.g., the formation of intra-strand DNA cross links), it is anticipated that all Pt anticancer drugs are potentially genotoxic. Cisplatin, carboplatin, and other Pt anticancer drugs have been shown to induce mutations in both in vitro and in vivo assays, although the mutagenic activity of cisplatin appears to be higher than that of the other Pt anticancer drugs (Sanderson et al., 1996).

A large database exists with strong evidence for genotoxic potential of cisplatin and other anticancer Pt compounds. For the Pt anticancer compounds, genotoxicity is determined by valency, conformation, and structure. Square planar *cis*-compounds, sush as cytostatic drug cisplatin, are the potent genotoxins and much more so than their *trans*-isomers. Furthermore, among anticancer Pt compounds there is evidence that Pt(IV) compound genotoxicity arises from reduction to its divalent Pt (II) species. Cisplatin[*cis*-$Pt(NH_3)_2Cl_2$] has been extensively studied as an anticancer therapeutic drug in the pharmaceutical industry.

The predominant toxic effects associated with the main parenteral Pt anticancer drugs and the oral drug JM216 are summarized in Table 4-10, along with other less predominant effects. The predominant toxic effect or effects are defined as those adverse effects that are considered dose-limiting for clinical use (e.g., due to the severe nature of the effect, higher doses cannot be administered). Treatment of patients with therapeutic doses of cisplatin and carboplatin has been associated with nephrotoxicity, neurotoxicity, ototoxicity, myelotoxicity, GI toxicity (primarily nausea and vomiting), and hypersensitivity. For cisplatin, the predominant toxic effects are nephrotoxicity, neurotoxicity, and ototoxicity, and for carboplatin, the predominant toxic effect is myelotoxicity. The predominant toxic effect associated with oxaliplatin is neurotoxicity, although myelotoxicity, GI toxicity, and hypersensitivity have also been reported with therapeutic use. All three of the parenteral drugs have been reported to induce hypersensitivity. Use of the experimental oral drug, JM216, in clinical trials has been consistently associated with myelotoxicity and GI toxicity, but the nephrotoxic, neurotoxic, and hypersensitization potentials of JM216 are uncertain due to conflicting reports and lack of information (see Table 4-10). This uncertainty may reflect the limited clinical experience with this drug.

Table 4-10. Toxic effects associated with Pt anticancer drugs

Toxicity	Cisplatin[a]	Carboplatin[a]	Oxaliplatin[a]	JM216
Nephrotoxicity	▲	●	●	●/—[b]
Neurotoxicity	▲	●	▲	●/ —[c]
Ototoxicity	▲	●	—	—[d]
Myelotoxicity	●	▲	●	▲[d]
GI toxicity	●	●	●	●[d]
Hypersensitivity	●	●	●	Not available

▲ Predominant toxic effect.
● Effect has been observed, but is not considered predominant.
— Toxic effect not observed.

[a]Hartmann and Lipp (2003).
[b]Sessa et al. (1998) stated that the nephrotoxicity of JM216 was "comparable to that of i.v. carboplatin in mice". McKeage (1995) reported that "JM216 exhibits "no nephrotoxicity" in animals or humans.
[c]Screnci and McKeage (1999) stated that JM216 has been "associated with infrequent peripheral neurotoxicity in early phase clinical trials." McKeage (1995) reported that JM216 exhibits "no peripheral neurotoxicity."
[d]McKeage (1995).

4.4.3.3. *Mode of Action for Nephrotoxicity of Pt Anticancer Drugs*

Information pertaining to the mode of action for nephrotoxicity is restricted to studies on Pt anticancer drugs. Cisplatin, carboplatin, and oxaliplatin are associated with nephrotoxicity in patients at standard therapeutic doses; however, cisplatin is considered to be the most nephrotoxic of these three drugs. It has been proposed that differences in nephrotoxic potency is related to differences in the renal handling of these drugs; cisplatin undergoes renal excretion by glomerular filtration and active proximal tubular secretion (Arany and Safirstein, 2003; Hartmann and Lipp, 2003; McKeage, 1995), whereas carboplatin and oxaliplatin do not appear to undergo significant tubular secretion (Hartmann and Lipp, 2003; Graham et al., 2000; Calvert et al., 1993). The principal site of cisplatin toxicity is the proximal tubule; thus, proximal tubular secretion of cisplatin provides a plausible pathway for entry of cisplatin into cells where degenerative tubular lesions are initially observed (Arany and Safirstein, 2003; Hartmann and Lipp, 2003; McKeage, 1995). Renal toxicity of cisplatin is reduced by administration of mannitol, which increases urine flow rate and thereby flushes the kidney and decreases the transit time of cisplatin in the kidney (WHO, 1991). Based on these observations, the renal accumulation and toxicity of cisplatin is likely related to renal transport mechanisms. Unlike carboplatin or oxaliplatin, renal tubular secretion is the major excretory pathway for cisplatin; thus, tubular epithelial damage is Pt compound-specific and may be related to the renal accumulation, urinary excretion, and renal tubular secretion of cisplatin (McKeage, 1995).

Although the mode of action of cisplatin-induced nephrotoxicity has not been identified, several possible mechanisms have been proposed. Like other nephrotoxic heavy metals (e.g., mercury), cisplatin is likely to interact with sulfhydryl compounds, leading to depletion of

intracellular glutathione and other protein and nonprotein sulfhydryls, and oxidant stress (Hartmann and Lipp, 2003; McKeage, 1995). Cisplatin also upregulates several cytokines in the kidney, leading to recruitment of inflammatory cells, which can injure surrounding renal tissue (Arany and Safirstein, 2003). Induction of gene products, possibly leading to apoptosis, has also been proposed to play a role in cisplatin-induced nephrotoxicity (Arany and Safirstein, 2003; Hartmann and Lipp, 2003).

Genotoxic damage by intercalation of DNA or oxidant-induced damage may also be an important component of stress-induced changes by cisplatin. The primary lesion produced by cisplatin in cancer cells is intrastrand binding to adjacent purine bases, which alters the secondary structure of DNA, inhibiting replication (Arany and Safirstein, 2003). This lesion is not produces by the *trans* isomer, which is neither nephrotoxic nor antineoplastic (Arany and Safirstein, 2003). It is unknown if cisplatin, or other Pt compounds, produces DNA damage in kidney cells.

In summary, information on the potential for Pt compounds to produce nephrotoxicity is limited to data on the Pt anticancer drugs. The nephrotoxic potential of the experimental oral Pt anticancer drugs has not been determined due to the limited clinical experience with these drugs. The precise mechanism of nephrotoxicity associated with Pt anticancer drugs has not been established, although nephrotoxic potency is compound-specific and appears to be related to renal excretory mechanisms and therefore, cisplatin has higher nephrotoxicity due to its unique renal excretion among Pt compounds studied. The relevance of the proposed mode of action derived for Pt anticancer drugs to induce nephrotoxicity is unknown for oral exposure to environmental forms of Pt compounds. Renal toxicity has not been associated with occupational exposure to Pt compounds. Additional information on the nephrotoxicity of other Pt compounds from the studies by Holbrook (1976) and Holbrook et al. (1975) indicates the possibility of kidney toxicity in rats exposed to $PtCl_4$ in drinking water (i.e., 8% increase in relative kidney weight); however, histopathological confirmation of kidney injury was not attempted in these studies and no data are available on the mechanisms of renal excretion for environmental Pt compounds. Thus, with the exception of the Pt anticancer drugs, the nephrotoxic potential for Pt compounds has not been established.

4.5. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

4.5.1. Sensitization Studies

4.5.1.1. *Soluble Pt Salts*

Animal studies have evaluated sensitization effects of halogenated Pt salts following inhalation, dermal, and parenteral exposure, providing limited evidence to support the numerous reports of allergic sensitization to halogenated Pt salts in groups of occupationally exposed workers. The results of the three available animal studies of inhalation exposure to Pt (Biagini et

al., 1986, 1985b, 1983) support the possibility that co-exposure to ozone may promote the development of allergic sensitization to halogenated Pt salts. Although inhalation exposure studies are the most relevant to occupational exposure, demonstration of sensitization by dermal and parenteral routes provides additional supportive data.

4.5.1.1.1. ***Inhalation studies.*** Sensitizing effects of inhaled halogenated Pt salts have been investigated in two subchronic exposure studies (Biagini et al.,1986, 1983) and one acute exposure study (Biagini et al.,1985b) in primates. The results of the acute exposure study are summarized in Section 4.4.1.2, *Acute Inhalation Exposure Studies,* and the subchronic exposure studies are described below.

Biagini et al. (1983) exposed groups of three or four cynomolgus monkeys to sodium hexachloroplatinate (Na_2PtCl_6) by nose-only inhalation at concentrations of 200 and 2,000 μg/m^3, 4 hours/day, biweekly, for 12 weeks. Reported MMADs and GSD for the aerosols were 1.61 μm and 2.03 for the low-exposure group and 1.27 μm and 2.09 for the high-exposure group. Another group of four monkeys was exposed biweekly for 12 weeks to a percutaneous dose of 20 mg Na_2PtCl_6 in water applied to a 7 × 7 cm shaved, abraded area (uncovered) on the intrascapular region of the back. The control group had eight nonexposed monkeys. Monkeys were evaluated pre- and postexposure with pulmonary function tests that included measurement of pulmonary resistance, dynamic compliance, PEF, FVC, FEVs, and FEFs 2 weeks following the end of exposure. Sodium hexachloroplatinate SPTs (administered to shaved areas of the chest and stomach) were administered pre- and postexposure with serially diluted doses of 1×10^{-3}–1×10^{-7} g/mL in saline given to monkeys pretreated for 15 minutes with an intravenous dose of 5% Evans blue dye. Baseline bronchoprovocation values were determined with a nebulized saline solution prior to provocation with Na_2PtCl_6.

No significant differences were seen in comparisons between pre- and postexposure SPTs to Na_2PtCl_6 in control or treated monkeys (Biagini et al., 1983). Postexposure measurements of pulmonary function following bronchoprovocation with nebulized saline showed no significant differences among groups. Bronchoprovocation with increasing doses of Na_2PtCl_6 (0–62.5 mg/mL) showed marked effects on pulmonary function in all control and treated animals when compared to baseline values. When bronchoprovocation data for the 62.5 mg/mL challenge dose of Na_2PtCl_6 were compared across groups, the pulmonary function parameters in the percutaneous and 2,000 μg/m^3 groups were not different than controls (monkeys in these three groups showed similar responses to Na_2PtCl_6). However, significant increases in pulmonary resistance and decreases in FEV in 0.5 seconds/FVC ratios were observed in the 200 μg/m^3 exposure group, when compared to controls. However, given the small number of animals in the control (n = 8), 200 μg/m^3 (n = 3), and 2,000 μg/m^3 (n = 4) groups, results of pulmonary function tests are difficult to interpret with respect to the dose-response relationship. This study showed that neither inhalation nor dermal exposure to Na_2PtCl_6 (at the doses used) for

12 weeks affected skin prick sensitivity or baseline pulmonary function in cynomolgus monkeys. Bronchoprovocation tests with Na_2PtCl_6 showed effects in all monkeys including controls, but these effects were more pronounced in the 200-μg/m^3 group.

In a follow-up study, Biagini et al. (1986) exposed groups of cynomolgus monkeys by inhalation to 200 μg/m^3 ammonium hexachloroplatinate ($[NH_4]_2PtCl_6$) (group 1, n = 8), 200 μg/m^3 $(NH_4)_2PtCl_6$ plus 1 ppm ozone (group 2, n = 8), or 1 ppm ozone alone (group 3, n = 7) for 6 hours/day, 5 days/week, for 12 weeks. Ozone was chosen for its ability to produce respiratory inflammation and irritation following inhalation. MMADs and GSDs for the aerosols were reported to be 0.94 μm and 2.03 for group 1 and 1.07 μm and 1.89 for group 2. Immediately after, and 2 weeks following exposure, animals were given methacholine and Na_2PtCl_6 bronchoprovocation tests and Na_2PtCl_6 SPTs. In addition, blood was collected for serum analysis for total and Pt-specific antibodies. No effects on animal health or body weight were observed. SPT to Na_2PtCl_6 conversion (from negative to positive) was seen in (positive tests/total tests) 1/8, 4/8, and 0/7 monkeys in groups 1, 2, and 3, respectively. No differences were seen in total IgE, total IgG, or Pt-specific IgE antibodies. Pulmonary function tests were normal among all monkeys following 12 weeks of exposure. However, Na_2PtCl_6 and methacholine challenge effects on pulmonary reactivity were significantly different from preexposure values in monkeys from group 2 ($[NH_4]_2PtCl_6$ plus ozone) but not groups 1 or 3. These results suggest a synergistic effect of inhalation exposure to $(NH_4)_2PtCl_6$ plus ozone on the development of sensitization to hexachloroplatinate. These results also provide support for the hypothesis that airway damage from exposure to irritant materials in combination with exposure to halogenated Pt salts may promote the development of allergic sensitization. Although no data are available on co-exposure to other relevant irritants or adjuvants such as diesel exhaust particles, the animal data suggesting that ozone promotes development of allergic sensitization to Pt supports the human data on increased probability of developing Pt hypersensitivity among smokers (Merget et al., 2000; Baker et al., 1990; Linnett and Hughes, 1999; see Section 4.1.2.1 for study details).

4.5.1.1.2. ***Dermal and parenteral studies.*** Exposure of volunteers and animals by dermal and parenteral routes also provide supportive evidence for the sensitization effects of halogenated Pt salts.

Results of a study on the passive transfer (via serum) of halogenated Pt salt-allergy to non-exposed humans and monkeys provide evidence of a possible IgG-mediated mechanism in the development of halogenated Pt salt allergy (Pepys et al., 1979). Serum was collected from six Pt refinery workers with positive SPT to $(NH_4)_2PtCl_6$ and ammonium "tetrachloroplatinite" (e.g., ammonium tetrachloroplatinate, or $(NH_4)_2PtCl_4$; as indicated in Table 2-1, tetrachloro-platinite is a synonym for tetrachloroplatinate); one worker was asymptomatic and five had work-related symptoms of asthma. Serum from each sensitized worker and from non-exposed

control subjects (number of control subjects was not reported) was injected 2.5 cm apart on the forearm of three male volunteers. After 24–48 hours, heat-treated serum (e.g., serum heated at 56°C for 2 hours) from the sensitized workers and controls were injected into the opposite forearm of the volunteers. SPTs with $(NH_4)_2PtCl_4$ were performed at the injection sites on both arms 3–4 hours after injection. For the passive transfer studies in monkeys, serum from sensitized and control workers was injected into sites on the thorax and abdomen of two male rhesus monkeys. After 24 hours, heat-treated serum was injected, and SPTs with $(NH_4)_2PtCl_4$ were performed 3–4 hours after injection. Positive SPT results to $(NH_4)_2PtCl_4$, as indicated by a wheal and flare response, were observed in all three volunteers injected with unheated sera; for two volunteers, a positive response was observed for sera from 4/6 sensitized workers, and for one volunteer, a positive response was observed for sera from 5/6 workers. The serum from each sensitized worker produced a positive SPT to $(NH_4)_2PtCl_4$ in at least one volunteer. Responses to sera from controls were not reported. For heat-treated serum, a flare-only response to SPT with $(NH_4)_2PtCl_4$ was observed in one volunteer for heat-treated sera from 3/6 workers, and no response to SPT with $(NH_4)_2PtCl_4$ was observed in the two other volunteers. In monkeys, no positive SPTs to $(NH_4)_2PtCl_4$ were observed. Using intracutanous injections of $(NH_4)_2PtCl_4$, a positive response was observed for sera from 2/6 sensitized workers in both monkeys, and positive results were observed for heat-treated sera from sensitized workers in one monkey (individual monkey data were not reported). The study authors hypothesized that the positive $(NH_4)_2PtCl_4$ SPT response to heat-treated sera may be due to the presence of a heat-stable antibody, such as IgG. However, involvement of an IgG-mediated mechanism, at least in some individuals, in the development of sensitization to halogenated Pt salts has not been established.

Schuppe et al. (1997a) evaluated the potential for Na_2PtCl_6 to induce hypersensitivity following repeated dermal applications in mice. Groups of 4–6 female naïve BALB/c mice were treated with 2.5 mg sodium hexachloroplatinate (Na_2PtCl_6) in acetone by topical application to the dorsum of both ears (1.25 mg applied to each ear; application area was not reported) for 4 consecutive days; the control group was treated with acetone. Mice were sacrificed 24 hours after the last treatment. An initial immune response was demonstrated by comparison of the number of cells with proliferating cell nuclear antigen ($PCNA^+$ cells) in fluid drained from auricular lymph nodes in treated compared to vehicle control animals. The total number of $PCNA^+$ cells in mice treated with Na_2PtCl_6 was 22.8 times greater than observed in control mice, indicating that dermal application of Na_2PtCl_6 induced an initial immune response. To evaluate the response to re-challenge with Na_2PtCl_6, naïve mice were initially sensitized by topical application (to the right ear only) of 0 or 1.25 mg Na_2PtCl_6 in acetone for 4 or 8 consecutive days. On weeks 1, 4, 8 (4-day group only), and 20 (8-day group only) following completion of the initial sensitizing treatment, a single re-challenge dose of 0 or 0.5 mg Na_2PtCl_6 in acetone was applied to the left ear; the response was evaluated by measuring left ear thickness 24 and 48 hours after re-challenge. At all re-challenge time points, a significant ($p < 0.05$ or 0.01,

compared to acetone re-challenge controls) increase in 24- and 48-hour left ear thickness was observed on re-challenge with Na_2PtCl_6 in the 4- and 8-day groups, with maximal left ear swelling at 48 hours ($p < 0.01$). No increase in ear thickness was observed in sensitized animal re-challenged with acetone only. Histological evaluation of left ear tissue 48 hours after re-challenge with Na_2PtCl_6 (4- or 8-day group not specified in the study report) showed dermal edema and infiltration of mononuclear and polymorphonuclear inflammatory cells. In contrast, a single application of 0.5 mg Na_2PtCl_6 or repeated application of acetone (number of doses were not reported) in naïve mice did not produce histopathological changes to ear tissue.

Topical application of ammonium tetrachloroplatinate, ammonium hexachloroplatinate, or cisplatin elicited a secretion profile of cytokines from cultured lymphocytes similar to secretion profiles elicited by other respiratory allergens such as trimellitic anhydride (TMA) (Dearman et al., 1998). Groups of female BALB/c mice (5 for each treatment groups and 10 for vehicle controls) were treated with 50 µL of ammonium tetrachloroplatinate ($[NH_4]_2PtCl_4$), ammonium hexachloroplatinate ($[NH_4]_2PtCl_6$), or cisplatin (*cis*-$[(NH_3)_2PtCl_2]$) (0, 0.25, 0.5, or 1% in DMSO). Solutions were applied to a shaved region (area of the application site was not reported) of the abdomen; a second treatment was administered after 5 days. On day 10 after the first treatment, 25 µL of the test solution was applied to the dorsum of each ear for 3 consecutive days. Concurrent controls were treated with 10% TMA or 1% 2,4-dinitrochlorobenzene (DNCB) in acetone and olive oil (AOO) or with AOO alone. Unlike DNB, TMA was previously shown to increase total serum IgE (indicating an IgE-mediated response). Auricular lymph nodes were drained 13 days after the initial treatment, and cells from the fluid were cultured. Culture media was analyzed for interleukin (IL)-4 and IL-10 (cytokines associated with initiation and maintenance of an IgE-mediated response) and INF-γ (a cytokine associated with inhibition of IgE antibody production) after 12, 24, and 48 hours in culture. In cells from mice treated with the three Pt compounds or TMA, dose-related increases in IL-4 and IL-10 production were observed (statistical significance not reported; data presented graphically); only a minimal response was observed for DNCB. In contrast, DNCB induced a pronounced production of INF-γ, whereas a much weaker response was observed for the three Pt compounds or TMA. These results are consistent with the human data indicating a Type I, IgE-mediated, immediate hypersensitivity mechanism of action for halogenated Pt salts.

Using the popliteal lymph node assay (PLN), Schuppe et al. (1992, 1997b) evaluated the sensitizing potencies of Pt compounds. All studies were conducted in the absence of adjuvant, and Pt compounds were administered as the free compound (e.g., the compounds were not conjugated to or co-administered with albumin).

Schuppe et al. (1992) evaluated the primary and secondary PLN response, including T cell-dependence, in a series of experiments. To evaluate the dose-response relationship of the primary PLN response to $(NH_4)_2PtCl_6$, groups of six C57BL/6 mice (sex not reported) were administered a single subcutaneous injection of 2, 9, 45, 90, 180, or 360 nmol (equivalent to 0.9,

4, 20, 40, 80, or 169 μg) of $(NH_4)_2PtCl_6$ in saline into one hind footpad; control mice received an injection of saline. Indices for weight and cell counts of PLNs (derived by comparison of the response of the injected versus untreated side for each animal) were determined on day 6 after injection (data presented graphically). Increases in PLN weight and total cell indices were observed, with statistically significant increases ($p \leq 0.05$ or 0.01) in both variables at doses ≥ 20 μg; maximal increases in weight and cell counts were observed at doses ≥ 40 μg. Similar results were observed for mice treated with sodium hexachloroplatinate (Na_2PtCl_6) (data were not presented in the study report). Evaluation of the time-course of the primary PLN response showed that maximal increases in PLN weight and cell count were observed 6 days after injection. In a study on the secondary PLN response, mice were primed with saline or 80 nmol (equivalent to 82 μg) Na_2PtCl_6 in saline by subcutaneous injection to one hind footpad and re-challenged 6 weeks later with saline or 36 nmol (equivalent to16 μg) Na_2PtCl_6 injected into the same footpad. The PLN count index in mice primed with Na_2PtCl_6 and re-challenged with Na_2PtCl_6 were significantly increased compared to mice primed with saline and challenged with the same dose of Na_2PtCl_6 (data were presented graphically; on day 2, $p \geq 0.005$; on day 6, $p \geq 0.05$), indicating a secondary PLN response. The primary PLN response appeared to be dependent on the presence of T cells. Following the same protocol for evaluation of the primary PLN response as described above, NMRI +/nu (T cell normal) and NMRI nu/nu (T cell deficient) mice were administered priming doses of 40, 80, or 169 μg $(NH_4)_2PtCl_6$ in saline or saline. The PLN cell count index was significantly ($p \leq 0.05$ or 0.01) increased at all priming doses of $(NH_4)_2PtCl_6$ in T cell normal mice compared to saline-primed mice, but no response was observed in T cell deficient mice (data presented graphically).

Schuppe et al. (1992) also compared the primary PLN response to $(NH_4)_2PtCl_6$ in the following strains of mice: BALC/c, DBA/2, C57BL/5, B10.S, C3H/He, and NMRI. Based on increases in PLN weight and cell count indices, all strains mounted a primary PLN response; BALC/c mice were highest responders, and B10.S, C3H/He, and NMRI were the lowest responders. The potency of Pt compounds to induce a primary PLN response was assessed in groups of 5–6 C57BL/5 and BALC/c mice (Schuppe et al., 1992). In C57BL/5 mice, equimolar doses (90 nmol) of Na_2PtCl_6 and $(NH_4)_2PtCl_6$ produced similar increases in the PLN cell count index (6.8 ± 1.2 and 6.2 ± 1.2 in the Na_2PtCl_6 and $(NH_4)_2PtCl_6$ groups, respectively; mean ± SD). In BALC/c mice, increases in the PLN cell count index were higher for $(NH_4)_2PtCl_6$ (9.3 ± 1.6) than for Na_2PtCl_6 (5.9 ± 1.0) (statistical significance was not reported). Also in BALC/c mice, 67 nmol cisplatin (the study report stated that higher concentrations were not available) produced a primary PLN response, with a cell count index of 3.8 ± 0.9 (*cis*-$[Pt(NH_3)_2Cl_2]$) was not assessed in C57BL/5 mice).

Results of the studies by Schuppe et al. (1992) demonstrate that Na_2PtCl_6, $(NH_4)_2PtCl_6$, and cisplatin, in the absence of adjuvant priming, induce an immune response in mice, and

suggest that T cells are required for a response to occur. Furthermore, the degree of response varies in magnitude across mouse strains.

Schuppe et al. (1997b) further explored the sensitizing properties of different Pt compounds in groups of 5–6 BALB/c mice. Using the PLN assay as described above (Schuppe et al., 1992), the potencies of equimolar doses (90 nmol) of Na_2PtCl_6, Na_2PtCl_4, or potassium tetrachloroplatinate (K_2PtCl_4), and of increasing doses (45–900 nmol) of tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) to induce a primary PLN response were evaluated on day 6 after priming injection. All Pt compounds were dissolved in saline; control mice were administered saline. Na_2PtCl_6, Na_2PtCl_4, and K_2PtCl_4 induced significant ($p \leq 0.01$) increases in the PLN cell count index compared to saline control (data presented graphically). For mice treated with $[Pt(NH_3)_4]Cl_2$, the cell count index was unaffected by treatment, except for a slight increase ($p \leq 0.05$) in mice treated with a 90 nmol dose; however, since no response was observed at substantially higher (up to 900 nmol) doses, the response to the 90 nmol dose was not considered to be treatment-related by investigators. Phenotyping of PLN cells showed that the majority of proliferating cells in mice treated with Na_2PtCl_6, Na_2PtCl_4, or K_2PtCl_4 were $CD4^+$ T cells.

Taken together, results of the studies by Schuppe et al. (1997b, 1992) demonstrate that Na_2PtCl_6, $(NH_4)_2PtCl_6$, Na_2PtCl_4, K_2PtCl_4, and *cis*-$[Pt(NH_3)_2Cl_2]$, in the absence of adjuvant priming, induce an immune response in mice; however, $[Pt(NH_3)_4]Cl_2$ did not exhibit immunogenic activity. The lack of immune response with $[Pt(NH_3)_4]Cl_2$ in the PLN assay in mice is consistent with results of the epidemiology study by Linnett and Hughes (1999) showing that no cases of sensitization were observed among 39 workers exposed to $[Pt(NH_3)_4]Cl_2$ in the production of automotive catalysts (study details provided in Section 4.1.2.1.2, *Toxicity of soluble forms of Pt: epidemiological evidence of Pt allergic sensitization*). Similar results were reported by Steinfort et al. (2008) in a prospective study of workers at a catalyst manufacture plant in Melbourne, Australia, where no cases of positive SPT were reported among workers with reported exposure to $[Pt(NH_3)_4]Cl_2$. However, the Linnett and Hughes (1999) and Steinfort et al. (2008) studies does not include exposure data on the particular Pt compounds to which workers are exposed and workers are instead classified by work area without speciated Pt exposure data. Results also suggest that the PLN response primarily involves T cells and may vary in magnitude with the specific mouse strain tested.

Immunoglobulin (IgE) responses to parenteral injections of Pt compounds ($[NH_4]_2PtCl_4$, $[NH_4]_2PtCl_6$, $[Pt(NH_3)_4]Cl_2$, $Cs_2Pt[NO_2]Cl_3$, $K_2Pt[CN]_4$, *cis*-$[Pt(NH_3)_2Cl_2]$) have been studied in the Hooded Lister rat (Murdoch and Pepys, 1986, 1985, 1984a, b).

Murdoch and Pepys (1984a) immunized female rats (6–8 animals per group) with intraperitoneal injections of a conjugate of Pt with bovine serum albumin (Pt-BSA) or ovalbumin (Pt-OVA). All animals received an intraperitoneal injection of heat-killed *Bacillus pertussis* (10^{10} bacilli) as adjuvant. The conjugates were formed by mixing BSA or OVA with an ammonium salt of $PtCl_4$ ($[NH_4]_2PtCl_4$), which yielded conjugates having a Pt content ranging

from approximately 1.7 to 9.9 moles Pt/mole protein. An initial dose of 100 μg of each conjugate was administered, followed by a boost dose of 10 μg of the conjugate. Corresponding Pt doses of the conjugates (initial 100 μg dose) ranged from 1.5 to 7.6 μg Pt, based on Table 1 of Murdoch and Pepys (1984a). Following immunization, serum was harvested and tested for activity in a passive cutaneous anaphylaxis (PCA) test in which female Hooded Lister recipients received an intradermal injection of serially diluted serum from the immunized rats, followed 24 hours latter by a challenge dose of 1 mg free halogenated Pt salt ($[NH_4]_2PtCl_4$) or conjugate, together with Evans blue dye (in 1% in saline), injected into the tail vein. PCA titers were assessed by observation of blueing of the dermal injection site, indicative of extravascular leakage of the dye from the vascular compartment and increased vascular permeability to macromolecules. Total serum IgE and Pt-specific serum IgE were determined in immunized rats. Pt-specific serum IgE was determined using a RAST specific for halogenated Pt salts ($[NH_4]_2PtCl_4$ conjugated to human serum albumin [HSA-Sephrose]). Injections of the free halogenated Pt salt failed to produce a response in the PCA test. Injections of Pt-BSA or Pt-OVA conjugates produced a response in the PCA test when the immunization and challenge were to homologous conjugates (i.e., Pt conjugated to the same protein) or to heterogeneous conjugates (i.e., Pt conjugated to protein different from the immunization). The PCA response appeared to be directed against the Pt moiety in the conjugates based on the following: (1) immunization with Pt-OVA resulted in a positive PCA response to Pt-BSA or Pt-OVA challenge, but no response to BSA alone; and (2) immunization with Pt-conjugates, but not with BSA or OVA alone, resulted in elevation in serum levels of Pt-specific IgE. Furthermore, the antibody response to Pt-BSA or Pt-OVA conjugates showed specificity to the conjugates relative to free halogenated Pt salt based on the observations that the response to a subsequent challenge dose of Pt-protein conjugates in the PCA assay was much greater than the response to injected $(NH_4)_2PtCl_4$ (i.e., a response to the free halogenated Pt salt was not detected in the PCA assay). Immunization with Pt-conjugates had no effect on total IgE levels in serum. These results suggest that Lister rats can develop Pt-specific antibodies to injected (intraperitoneal) Pt-BSA or Pt-OVA conjugates and that the antibody response shows specificity to the Pt moiety of the conjugates.

Murdoch and Pepys (1984b) examined the effect of Pt compounds on sensitization of rats to OVA. Female Hooded Lister rats (6–8 animals per group) were immunized with intraperitoneal injections of OVA alone or OVA together with one of the following Pt compounds (OVA and Pt were injected at different sites to avoid conjugation): $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$, $[Pt(NH_3)_4]Cl_2$, *cis*-$PtCl_2(NH_3)_2$, or $Cs_2[Pt(NO_2)Cl_3]$. Doses were 10, 100, or 1,000 μg compound; the corresponding Pt doses for the 10 μg dose of each compound were approximately: 5.1, 4.4, 5.8. 6.5, or 3.2 μg Pt, respectively. All animals received heat-killed *B. pertussis* (10^{10} bacilli/animal) as adjuvant. Animals received a boost injection of OVA 21 days following the initial immunization. Following the initial and boost immunization, serum

was harvested and tested for activity in a PCA test in which OVA was the challenge antigen. Total serum IgE and OVA specific serum IgE (RAST) were determined in immunized rats. Immunization with OVA together with Pt compounds produced an enhanced response in the PCA assay, compared to the response that followed immunization with OVA alone. The enhanced response was evident after immunization with $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$, or $Cs_2[Pt(NO_2)Cl_3]$ and only after the boost injection of OVA. Sensitization was not detected following immunization with OVA together with $[Pt(NH_3)_4]Cl_2$. Immunization with *cis*-$PtCl_2(NH_3)_2$ resulted in reduced antibody response in the PCA test, which was attributed to observed toxicity in the immunized rats (i.e. weight loss). Immunization with OVA together with $(NH_4)_2PtCl_4$ or $(NH_4)_2PtCl_6$ resulted in enhanced serum levels of OVA-specific IgE. Immunization with Pt compounds had no enhancing effect on total IgE levels in serum. These results suggest that Lister rats can develop antibodies to injected (intraperitoneal) OVA and that this response is enhanced by co-administration of OVA and certain Pt-compounds. The responses occurred with $(NH_4)_2PtCl_4$ and $(NH_4)_2PtCl_6$, and to a lesser extent with $Cs_2[Pt(NO_2)Cl_3]$ (this compound did not produce an enhancement of serum OVA-specific IgE levels).

Murdoch and Pepys (1986) examined the kinetics of the IgE response to repeated doses of $(NH_4)_2PtCl_4$ in animals sensitized to OVA. Female Hooded Lister rats (8 animals per group) were immunized with intraperitoneal injections of OVA alone or OVA together with $(NH_4)_2PtCl_4$. Doses were not reported and were noted to have been optimized for an IgE response, based on previous studies (Murdoch and Pepys, 1984b). OVA was injected on days 1 and 21 (boost), without adjuvant (heat-killed *B. pertussis* and/or aluminum hydroxide gel). The Pt compound was injected once (day 1) or 3 times/week for 3 weeks. Following immunization, serum was harvested and tested for total serum IgE and IgG, and OVA-specific serum IgE (RAST), and activity in a PCA test in which OVA was the challenge antigen. Injection of adjuvant alone had no effect on serum total IgE levels. Injection of $(NH_4)_2PtCl_4$, in the absence of adjuvant treatment, had no effect on total serum IgE levels. A single injection of $(NH_4)_2PtCl_4$ together with adjuvant also had no effect in total serum IgE; however, repeated injections of $(NH_4)_2PtCl_4$ elevated serum total IgE and OVA-specific IgE. The enhanced IgE response increased in magnitude with repeated dosing with $(NH_4)_2PtCl_4$ and declined after cessation of dosing. Activity on the PCA test correlated ($r = 0.892$) with serum OVA-specific IgE. These results show that the enhanced IgE response to injected (intraperitoneal) OVA produced by $(NH_4)_2PtCl_4$ increases with repeated dosing and declines after cessation of the exposure.

Murdoch and Pepys (1985) examined cross-reactivity of IgE antibodies produced in response to immunization with Pt-OVA conjugate to various Pt compounds. Female Hooded Lister rats (number of animals per group was not reported) were immunized with intraperitoneal injections of a Pt-OVA conjugate prepared from OVA and $(NH_4)_2PtCl_4$, together with heat-killed *B. pertussis* (10^{10} bacilli/animal) as adjuvant. The conjugates had a Pt content ranging from 5 to

8 moles Pt/mole protein. An initial dose of 100 μg of each conjugate was administered, followed by a boost dose of 10 μg. Following the initial and boost immunization, serum was harvested and tested for activity in a PCA test in which the challenge dose was either 50 μg of Pt-BSA conjugate or 50 μg of one of the following Pt compounds: $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$, $Cs_2[Pt(NO_2)Cl_3]$, $[Pt(NH_3)_4]Cl_2$, $K_2Pt(CN)_4$, or *cis*-$PtCl_2(NH_3)_2$. The corresponding Pt doses of the free (i.e., not conjugated) Pt compounds were approximately 26.2, 22.0, 15.9, 29.2, 25.8, or 32.5 μg, respectively. Pt-specific serum IgE (RAST) levels were determined in immunized rats. Immunization with Pt-OVA resulted in a positive response on the PCA test to a challenge with Pt-BSA conjugate, $(NH_4)_2PtCl_4$, or $(NH_4)_2PtCl_6$, and negative response to a challenge with $Cs_2[Pt(NO_2)Cl_3]$, $[Pt(NH_3)_4]Cl_2$, $K_2Pt(CN)_4$, or *cis*-$PtCl_2(NH_3)_2$. Immunization with Pt-OVA conjugate resulted in enhanced serum levels of Pt-specific IgE, which cross-reacted with both Pt-OVA and Pt-BSA conjugate (RAST inhibition). These results suggest that Lister rats can develop antibodies to injected (intraperitoneal) Pt-OVA conjugate and that this response sensitizes the rats to both Pt-BSA conjugates as well as free $(NH_4)_2PtCl_4$ and $(NH_4)_2PtCl_6$. The cross-reactivity of the antibodies produced in response to immunization with Pt-OVA is more pronounced with free $(NH_4)_2PtCl_4$ and $(NH_4)_2PtCl_6$ than with $Cs_2[Pt(NO_2)Cl_3]$, $[Pt(NH_3)_4]Cl_2$, $K_2Pt(CN)_4$, or *cis*-$PtCl_2(NH_3)_2$ (i.e., no reactivity was detected with the latter four Pt-compounds in this study).

In summary, the studies conducted by Murdoch and Pepys (1986, 1985, 1984a, b) in the Hooded Lister rat provide evidence that intraperitoneal injection of Pt-compounds, either as protein-conjugates or as free halogenated Pt salts, can trigger production of IgE-specific antibodies that sensitize the animal to subsequent exposures to the Pt compounds. Specific findings from these studies that support this conclusion are as follows:

(1) Immunization of rats with intraperitoneal doses of Pt-protein conjugates (e.g., Pt-OVA, Pt-BSA) results in sensitization to heterologous challenge with Pt-protein conjugates.

(2) Antibodies produced in response to immunization with Pt-OVA cross-react with Pt-BSA, $(NH_4)_2PtCl_4$, or $(NH_4)_2PtCl_6$ and to a lesser extent (if at all) to $Cs_2[Pt(NO_2)Cl_3]$, $[Pt(NH_3)_4]Cl_2$, $K_2Pt(CN)_4$, or *cis*-$PtCl_2(NH_3)_2$.

(3) Sensitization of rats to OVA can be enhanced by injections of the free halogenated Pt salts $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$, or $Cs_2[Pt(NO_2)Cl_3]$, and to a lesser extent (if at all) to $[Pt(NH_3)_4]Cl_2$, *cis*-$PtCl_2(NH_3)_2$; the enhanced sensitization to OVA that occurs with $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$, or $Cs_2[Pt(NO_2)Cl_3]$ is further increased with repeated doses of the Pt compounds.

(4) The above responses were observed only in animals that received adjuvant and were more pronounced for the more highly chlorinated Pt compounds examined in these studies (e.g., $[NH_4]_2PtCl_4$ or $[NH_4]_2PtCl_6$) compared to less chlorinate compounds (e.g., $Cs_2[Pt(NO_2)Cl_3]$, $[Pt(NH_3)_4]Cl_2$ $K_2Pt[CN]_4$, *cis*-$PtCl_2[NH_3]_2$).

The lack of sensitization following immunization with OVA together with $[Pt(NH_3)_4]Cl_2$ is consistent with results of Schuppe et al. (1997b) in mice showing the lack of immune response with $[Pt(NH_3)_4]Cl_2$ in the PLN assay and results of the epidemiology study by Linnett and Hughes (1999) showing that no cases of sensitization were observed among 39 workers exposed to $[Pt(NH_3)_4]Cl_2$ in the production of automotive catalysts (study details provided in Section 4.1.2.1.2, *Toxicity of soluble forms of Pt: epidemiological evidence of Pt allergic sensitization*).

4.5.1.1.3. ***In vitro studies: effects on human immune cells in culture.*** The in vitro effects of several Pt compounds ($[NH_4]_2PtCl_6$, $[NH_4]_2PtCl_4$, $PtCl_4$, $PtCl_2$, sodium hexaiodoplatinate $[Na_2PtI_6]$, and cisplatin) on spontaneous and phytohemagglutin (PHA)-stimulated proliferation of human peripheral blood mononuclear cells (PBMC; PBMC cells are a mix lymphocytes and monocytes, including B and T immune cells) and release of several cytokines, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-5 were evaluated at low (10^{-7} M) and high (10^{-4} M) concentrations (Di Gioacchino et al., 2004). Low concentrations of $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ inhibited both spontaneous and PHA-stimulated PBMC proliferation and low concentrations of cisplatin inhibited PHA-stimulated proliferation. No effects on spontaneous or PHA-stimulated proliferation were observed for $PtCl_4$, $PtCl_2$, or Na_2PtI_6. TNF-α release was inhibited only by the high concentration of $(NH_4)_2PtCl_6$. IFN-γ release was inhibited by low and high concentrations of $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ and the high concentration of Na_2PtI_6. IL-5 release was inhibited at the high concentration for $(NH_4)_2PtCl_6$, $(NH_4)_2PtCl_4$, and Na_2PtI_6 and enhanced for the low and high concentrations of $PtCl_4$. $PtCl_2$ did not affect cytokine release. These results indicate the following potency for immune cell responses of the tested Pt compounds: $(NH_4)_2PtCl_6 > (NH_4)_2PtCl_4 > Na_2PtI_6$ and cisplatin > $PtCl_4 > PtCl_2$. Thus, cells involved in the sensitization response may be directly affected by Pt compounds.

An in vitro study of Pt and PGEs was conducted to investigate the effect of PGEs on antigen presentation by human dendritic cells, and explore the potential role of dendritic cells in generating an allergic response to PGEs (Paolucci et al., 2007). Monocyte-derived human dendritic cells were obtained from peripheral blood samples from healthy donors and incubated under appropriate culture conditions to produce mature and immature dendritic cells. Dendritic cells were cultured in the presence of 10 μM concentrations of the following Pt, palladium, and rhodium compounds: $Na_2PtCl_4 \cdot 3H_2O$, $Na_2PtCl_6 \cdot 6H_2O$, Na_2PdCl_4, $Na_2PdCl_6 \cdot 6H_2O$, $RhCl_3$, $Na_3RhCl_6 \cdot 12H_2O$. Preliminary experiments were performed on all six PGEs and the hexachlorinated compounds of Pt, palladium, and rhodium were then used to treat dendritic cells prior to measuring several markers of dendritic cell activation: expression of cell membrane differentiation markers (CD80, CD86, and major histocompatibility complex [MHC]-II), expression of the high affinity receptor Fcε-RI, antigen presentation of grass pollen (in co-cultures of T cells, dendritic cells, and raw grass pollen from individuals allergic to grass pollen),

and endocytosis. All three PGEs increased expression of CD 86 (a T-cell activator), Na_2PtCl_6 and Na_2PdCl_6 increased expression of CD80 (a co-stimulator and T-cell activator), and $Na_2PtCl_6 \cdot 6H_2O$ also increased cell surface expression of MHC-II. Incubation with Na_2PtCl_6 and Na_2PdCl_6 increased the T-cell proliferation in the presence of grass pollen, suggesting that both compounds increase the efficiency of antigen presentation to antigens for existing allergies. Na_2PtCl_6 increased endocytosis by mature dendritic cells, but did not affect immature cells. All three PGEs also increased the expression of Fcε-RI, increased the production of IL-5, and had no effect on IL-4 or INF-γ. The authors conclude that PGEs have an adjuvant-like effect on human dendritic cells that may increase the response to allergens.

In vitro exposure to hexachloroplatinic acid (H_2PtCl_6) (0.025–25 μM) has been shown to enhance reactive oxygen species (ROS) production in human neutrophils as measured by lucigenin-enhanced chemiluminescence (Theron et al., 2004). Extracellular ROS production from neutrophils or phagocytes in general has been implicated in bronchial hyperresponsiveness in some cases of asthma (Barnes, 1989). In the presence of H_2PtCl_6, neutrophils also inactivated α1-proteinase inhibitor (API) (Theron et al., 2004). API is involved in the protection of airways from infective and inflammatory insult, and reductions in API are associated with bronchitis and asthma (Hiemstra, 2002; Stockley et al., 2002). The in vitro H_2PtCl_6-induced ROS production by neutrophils takes place in the absence of traditional markers of neutrophil proinflammatory reactions such as the generation of eicosanoids and prostanoids, the release of the granule enzyme elastase, or the mobilization of Ca^{2+} from either intracellular or extracellular stores. Rather than pro-inflammatory, Theron et al. (2004) characterized the effects of H_2PtCl_6 as pro-oxidative actions dependent on intact neutrophil NADPH oxidase and attenuated by inhibitors of the electron transporter. Similar pro-oxidative interactions with neutrophils were also found with palladium, but not with the Pt compound, cisplatin, or other PGEs (rhodium and osmium).

4.5.1.2. *Insoluble Pt Forms*

As reviewed earlier in Section 4.1, insoluble forms of Pt (Pt metal and PtO_2) are generally considered to be inert (ACGIH, 2001; Gebel, 2000; WHO, 2000, 1991). Limited supportive evidence that insoluble Pt compounds are inactive as sensitizing agents is provided by results of the in vitro study by Di Gioacchino et al. (2004), showing that $PtCl_2$ does not have immune effects on human PBMC proliferation or cytokine release. No additional studies on the potential allergenic effects of inhaled insoluble Pt compounds were identified.

In acute exposure experiments, mice (either 8 weeks or 18 months of age) exposed for 6 hours to ultrafine Pt metal particles at inhaled concentrations of about 110 μg Pt/m^3 showed no inflammatory responses in the lungs (Oberdörster, 2001). Pt metal particles in the test atmospheres were reported to have count median diameters of approximately 25 nm. When pretreated with an intratracheal instillation of elastase to induce emphysema, the young mice still showed no signs of pulmonary inflammation following 6 hours of exposure, but the aged mice

showed a mild inflammatory response in the lungs (a slight increase in neutrophil count and the appearance of microscopic lymphocytic infiltrations around the peribronchiolar spaces). No additional studies regarding the potential irritation effects of inhaled insoluble Pt compounds were identified.

Although data are lacking regarding the potential of inhaled insoluble Pt compounds to produce sensitization effects, it is possible that repeated exposure to dusts of Pt metal or Pt oxides can lead to respiratory irritation, inflammation, or other more serious respiratory lesions, especially at concentrations that overload respiratory clearance mechanisms, as has been observed with other relatively insoluble and inert airborne materials (see Li et al., 1996; Oberdörster, 1994). Particle overload, which results from altered macrophage clearance of inhaled particles, is associated with enhanced lung accumulation of particles, pulmonary inflammation, and epithelial cell proliferation (ILSI, 2000). As a result of increased accumulation, the potential for local adverse effects is enhanced. Thus, for insoluble and poorly soluble particulate compounds, exposure levels leading to particle overload may result in increased toxicity. Data on toxicity and clearance of soluble and insoluble compounds of another metal, nickel, in rodents suggest a role for particle overload in toxicity of insoluble metal particulates (Hsieh et al., 1999a, b); however, data on potential particle overload for insoluble Pt compounds are not available (see Section 3.1.2 and 3.2.2 for discussion of available studies). The relevance of rodent data on particle overload to humans is unclear as rodent species may be more susceptible than larger mammals and humans to alterations in pulmonary clearance that result in increased retention of insoluble particles (Snipes, 1996).

4.5.2. Genotoxicity Studies

Several Pt compounds have been studied for their genotoxic potential, although the database is limited. The available studies on the genotoxicity of Pt compounds include comparisons of the activities of Pt compounds in mutation assays with *Escherichia coli* (Gebel et al., 1997; Kanematsu et al., 1980; LeCointe et al., 1979), *Salmonella typhimurium* (Uno and Morita, 1993; Kanematsu et al., 1980; LeCointe et al., 1979), *Bacillus subtilis* (Kanematsu et al., 1980), Chinese hamster ovary (CHO) cells at the HGPRT locus (Johnson et al., 1980; Taylor et al., 1979a) and mouse lymphoma cells at the TK locus (Sandhu, 1981). Also available are studies on micronuclei formation in human lymphocytes (Gebel et al., 1997), meiotic disturbance in *Saccharomyces cerevisiae* (Sora et al., 1986), and enhancement of transformation of Syrian hamster embryo cells by an adenovirus, SA7 (Casto et al., 1979). Results from these studies are summarized in Table 4-11.

Table 4-11. Summary of genotoxicity studies of Pt compounds

In vitro gene mutation assays							
Test compound	**Test system**	**Cells/strain**	**Concentration**	**Results**		**Comments**	**Reference**
				-S9	**+S9**		
K_2PtCl_4	*S. typhimurium* (reverse mutations)	TA100	Not specified	+	NP		LeCointe et al., 1979
	S. typhimurium (reverse mutations)	TA98, TA100	0.8–100 nmol/plate	+	+		Uno and Morita, 1993
	E. coli (SOS chrome test)	PQ37	6–781 µM	+	NP	50% cytotoxicity ≥391 µM	Gebel et al., 1997
	Bacteriophage λ (forward mutation to virulence in *E. coli*)	λGY14 in lysogenic *E. coli* GY4854 and indicator strain GY3646	Not specified	-	NP		LeCointe et al., 1979
	S. cerevisiae (meiotic disturbance–disomic or diploid spores)	DIS13	5–100 µM	+	NP	(increased diploid only)	Sora et al., 1986
	CHO cells (HGPRT locus)	CHO	0–65 µM	+/-	NP		Johnson et al., 1980
	CHO cells (mutations at the HGPRT locus)	CHO-S, auxotrophic for proline	1–200 µM	-	NP		Taylor et al., 1979a
	Human peripheral lymphocytes (micronuclei)	Lymphocyte	5–300 µM	+	NP		Gebel et al., 1997
$PtCl_4$	*S. typhimurium*	TA1535, TA100, TA98, TA1537, TA1538	Not specified	+	NP	+ in TA 98	Kanematsu et al., 1980
	E. coli (reverse mutations, spot test)	WP2 *hcr*$^-$ *try*$^-$	Not specified	-	NP		Kanematsu et al., 1980
	E. coli (SOS chrome test)	PQ37	8–481 µM,	+	NP	50% cytotoxicity ≥120 µM	Gebel et al., 1997
	B. subtilis (rec assay)	H17 (rec$^+$), M45 (rec$^-$)	5–500 mM	+	NP	effective concentration = 1mM	Kanematsu et al., 1980
	D. melanogaster (sex-linked recessive lethal mutations)	Canton-S males	0.3 mM for 72 hr or 1.5 mM for 48 hr	+	NP	in feeding solution	Woodruff et al., 1980
	Mouse lymphoma cells (forward mutation at the TK locus)	L5178Y	50–100 µM	+	NP		Sandhu, 1979
	Human peripheral lymphocytes (micronuclei)	Lymphocyte	10–60 µM	+	NP		Gebel et al., 1997
	Syrian hamster embryo cells (enhancement of transformation by adenovirus, SA7)	SHE	15–120 µM	+	NP		Casto et al., 1979

Table 4-11. Summary of genotoxicity studies of Pt compounds

In vitro gene mutation assays							
Test compound	**Test system**	**Cells/strain**	**Concentration**	**Results**		**Comments**	**Reference**
				-S9	**+S9**		
H_2PtCl_6	*S. typhimurium*	TA98, TA100	0.8–100 nmol/plate	-	+	+ with S9 in TA 98	Uno and Morita, 1993
	B. subtilis (rec assay)	H17 (rec^+), M45 (rec^-)	5–500 mM	+	NP	effective concentration = 10 mM	Kanematsu et al., 1980
K_2PtCl_6	*E. coli* (SOS Chromotest)	PQ37	11–367 µM	-	NP	50% cytotoxicity ≥92 µM	Gebel et al., 1997
	S. typhimurium	TA97a, TA98, TA100, TA102	5–500 µg/plate	+	+	- without S9 in TA97a	Bunger et al., 1996
K_2PtBr_6	*S. typhimurium* (reverse mutations)	TA98, TA100	0.8–100 nmol/ plate	-	-		Uno and Morita, 1993
$(NH_4)_2PtCl_6$	*S. typhimurium*	TA1535, TA100, TA98, TA1537, TA1538	Not specified	+	NP	+ in TA98, others inconclusive	Kanematsu et al., 1980
	S. typhimurium	TA97a, TA98, TA100, TA102	5–500 µg/plate	+	+		Bunger et al., 1996
	B. subtilis (rec assay)	H17 (rec^+), M45 (rec^-)	5–500 mM	+	NP	effective concentration = 100 mM	Kanematsu et al., 1980
$(NH_4)_2PtCl_6$	*E. coli* (reverse mutations, spot test)	WP2 *hcr*$^-$ *try*$^-$	Not specified	+	NP		Kanematsu et al., 1980
		B/r WP2 try^-	Not specified	-	NP		Kanematsu et al., 1980
$(NH_4)_2PtCl_4$	*S. typhimurium*	TA97a, TA98, TA100, TA102	5–500 µg/plate	+	+		Bunger et al., 1996
$[Pt(NH_3)_4]Cl_2$	*S. typhimurium* (reverse mutations)	TA100	Not specified	-	NP		LeCointe et al., 1979
	S. typhimurium	TA98, TA100	0.8–100 nmol/ plate	-	-		Uno and Morita, 1993
	Bacteriophage λ (forward mutation to virulence in *E. coli*)	λGY14 in lysogenic *E. coli* GY4854 and indicator strain GY3646	Not specified	-	NP		LeCointe et al., 1979
	CHO cells (mutations at the HGPRT locus)	CHO	0–6,600 µM	-	NP		Johnson et al., 1980

Table 4-11. Summary of genotoxicity studies of Pt compounds

In vitro gene mutation assays							
Test compound	**Test system**	**Cells/strain**	**Concentration**	**Results**		**Comments**	**Reference**
				-S9	**+S9**		
$PtCl_2$	*E. coli* (SOS Chromotest)	PQ37	19–1,213 µM	-	NP	50% cytotoxicity ≥606 µM	Gebel et al., 1997
	Mouse lymphoma cells (forward mutation at the TK locus)	L5178Y	50–800 µM	-	NP		Sandhu, 1979
$Pt(NH_3)_2(NO_2)_2$ $Pt(SO_4)_2$	Mouse lymphoma cells (forward mutation at the TK locus)	L5178Y; CHO-S, auxotrophic for proline	1–200 µM	-	NP		Sandhu, 1979
	CHO cells (mutations at the HGPRT locus)		1–500 µM	+	NP		Taylor et al., 1979a

+ = Positive; - = negative/no change; NP = assay not performed

Mutagenic properties of 16 Pt compounds were studied using *S. typhimurium* TA98 and TA100 (Uno and Morita, 1993). Mutagenic activity was found in some Pt compounds, including $Pt(C_5H_{12}N_2)Cl_2$, $Pt(en)Cl_2$, $[Pt(NH_3)_3Cl]_2PtCl_4$, and $K_2[PtCl_4]$, both in the presence and absence of S9 mix in TA98 and TA100 strains. When the same compounds were tested using a different solvent, DMSO, it was found that they were much less mutagenic and less toxic compared to distilled water as a solvent for both TA98 and TA100 strains. Other compounds such as $Ba[Pt(CN)_4].4H_2O$, $K_2[PdCl_4]$, *cis*-$pt(NH_3)_2(NO_2)_2$, $K_2[Pt(C_2O_4)_2].2H_2O$, $[Pt(NH_3)_4]Cl_2$, and $K_2[Pt(NO_2)_4].H_2O$ did not show significant mutagenicity in either strain with or without S9 mix (Uno and Morita, 1993). The authors suggest two possibilities for this difference in the result. It is possible that the structure of the Pt complex in DMSO is different from that in distilled water. Displacement of the chloride ligant with DMSO can occur when they are dissolved in DMSO, giving ionic species that react less strongly with bacteria. It is also possible that the bacterial susceptibility is changed in the presence of a solvent quantity of DMSO.

Three halogenated Pt salts [K_2PtCl_6, $(NH_4)_2PtCl_4$, $(NH_4)_2PtCl_6$] were evaluated for mutagenicity using *S. typhimurium* strains (TA97a, TA98, TA100, and TA102) both in the presence and absence of metabolic activation. All three compounds caused higher rates of reverse mutation in all of the tester strains, but $(NH_4)_2PtCl_4$ was the most potent among the three compounds tested. Cytotoxicity of these Pt compounds was analyzed using mouse fibroblasts (L929) and human embryonic lung (L132) cell lines. Cytotoxic effects of the three Pt complexes, measured as ED_{50}, occurred at test concentration of 0.2 mM (Bunger et al., 1996).

Gebel et al. (1997) compared several Pt compounds in the bacterial SOS chromotest using *E. coli* PQ37 and have shown the following order for the induction of β-galactosidase activity, an index for DNA repair mechanisms induced in response to DNA damage (induction factor values [fold increases from controls] are noted in parentheses): $PtCl_4$ (4.54) > K_2PtCl_4

(3.63) > $PtCl_2$ (1.42) > K_2PtCl_6 (1.01). The mechanism of mutagenic activity is believed to occur through the reaction with DNA by displacement of both chlorine atoms and subsequent chelate formation between N7(G) and O6(G) sites. Gebel et al. (1997) also performed micronucleus (MN) assay in human peripheral lymphocytes from healthy donors aged 25–35 years using various Pt compounds. A significant increase in number of MN was obtained in $PtCl_4$ exposed cells to different concentrations (0–60 μM). A significant increase in MN was also observed in K_2PtCl_4 compound at higher dose (150 μM) tested. The highest dose (300 μM) was toxic. No significant increase in MN was observed in two other Pt compounds tested (K_2PtCl_6 and $PtCl_2$). The order of potency for these compounds with respect to the induction of micronuclei in primary cultures of human peripheral lymphocytes (lowest effective concentrations are noted in parentheses): $PtCl_4$ (20 μM) > K_2PtCl_4 (150 μM). As mentioned above, neither $PtCl_2$ nor K_2PtCl_6 induced micronuclei in these assays (Gebel et al., 1997).

Male *Drosophila melanogaster* were treated by feeding 0.3 or 1.5 mM $PtCl_4$ (n = 33 versus n = 29 in controls) in a 1% glucose solution for either 72 or 48 hours, respectively, with an objective of identifying recessive sex-linked lethal mutations as a result of exposure to $PtCl_4$ (Woodruff et al., 1980). Both 0.3 and 1.5 mM treatments with $PtCl_4$ induced significant increases in recessive lethal mutations compared to control frequencies. $PtCl_4$ was also tested for induction of mutation (TK locus) in mouse lymphoma cells (Sandhu, 1979). $PtCl_4$ induced mutation frequencies at doses ranging from 25 to 150 μM that were significantly greater than the spontaneous mutation frequencies.

Pt compounds showing mutagenic activity with the available data: $PtCl_4$, K_2PtCl_4

Results from various genotoxicity assays support the findings by Gebel et al. (1997) that $PtCl_4$ and K_2PtCl_4 have genotoxic potential. $PtCl_4$ induced mutations in mouse lymphoma cells (Sandhu, 1979), in *D. melanogaster* (Woodruff et al., 1980), and in *S. typhimurium* strain TA98, but not in strains TA100, TA1535, TA1537, or TA1538 (Kanematsu et al., 1980). $PtCl_4$ also induced micronuclei in human peripheral lymphocytes (Gebel et al., 1997). $PtCl_4$ enhanced transformation of Syrian hamster embryo cells by the adenovirus, SA7 (Casto et al., 1979), and produced positive results in the *B. subtilis* rec assay at lower concentrations than H_2PtCl_6 or $(NH_4)_2PtCl_6$ (Kanematsu et al., 1980), but did not induce mutations in *E. coli* strain WP2 *hcr*$^-$ *try*$^-$ (Kanematsu et al., 1980). K_2PtCl_4 induced diploid spores in *S. cerevisiae* strain DIS13 (Sora et al., 1986) and mutations in *S. typhimurium* strains TA98 and TA100 (Uno and Morita, 1993; LeCointe et al., 1979), but did not consistently induce mutations at the HGPRT locus in CHO cells (Johnson et al., 1980; Taylor et al., 1979a) or in the bacteriophage λ assay (LeCointe et al., 1979). In addition, $Pt(SO_4)_2$ may also have some genotoxic potential, as evidenced by the finding that it induced mutations in CHO cells (Taylor et al., 1979a). However, this conclusion is based on only one study that is currently available.

Pt compounds without significant mutagenic activity: $PtCl_2$, H_2PtCl_6, $[Pt(NH_3)_4]Cl_2$, K_2PtBr_6, K_2PtCl_6

Studies conducted on $PtCl_2$ and tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) consistently have shown no significant genotoxic activities. $PtCl_2$ did not induce mutations at the TK locus in mouse lymphoma cells (Sandhu, 1979) or at the HGPRT locus in CHO cells (Taylor et al., 1979a). $[Pt(NH_3)_4]Cl_2$ did not induce HGPRT mutations in CHO cells (Johnson et al., 1980), reverse mutations in *S. typhimurium* strains TA 98 or TA100 (Uno and Morita, 1993; LeCointe et al., 1979), or mutations in the bacteriophage λ assay (LeCointe et al., 1979). Available data on most chloroplatinate compounds present little evidence of genotoxicity potential and, in some cases, present conflicting evidence from the limited available studies. H_2PtCl_6 did not consistently induce mutations in *E. coli* strain WP2 *hcr*$^-$ *try*$^-$ (Kanematsu et al., 1980) or in several strains of *S. typhimurium* (Uno and Morita, 1993; Kanematsu et al., 1980), but did produce positive results in the *B. subtilis* rec assay (Kanematsu et al., 1980). $(NH_4)_2PtCl_6$ induced mutations in *E. coli* strain WP2 *hcr*$^-$ *try*$^-$ (Kanematsu et al., 1980) and *S. typhimurium* strain TA98, but not in strains TA100, TA1535, TA1537, or TA1538 (Kanematsu et al., 1980). $(NH_4)_2PtCl_6$ produced positive results in the *B. subtilis* rec assay at a concentration that was 100-fold higher than the lowest effective concentration for $PtCl_4$ (Kanematsu et al., 1980). $(NH_4)_2PtCl_6$ and $(NH_4)_2PtCl_4$ induced mutations in *S. typhimurium* strains TA97a, TA98, TA100, and TA102 (Bunger et al., 1996). K_2PtCl_6 did not induce mutations at the HGPRT locus in CHO cells (Taylor et al., 1979a). K_2PtCl_6 did, however, induce mutations in *S. typhimurium* strains TA97a, TA98, TA100, and TA102 (Bunger et al., 1996). K_2PtBr_6 (a hexabromoplatinate salt) did not induce mutations in *S. typhimurium* strains TA 98 or TA100 (Uno and Morita, 1993), but no other genotoxicity data were found for this compound.

A large database exists with strong evidence for genotoxic potential of cisplatin and other anticancer Pt compounds. Because they are not environmentally relevant compounds, the studies related to genotoxic potential of cisplatin and other anticancer Pt compounds are not discussed in this toxicological review.

In summary, several Pt compounds have been tested for their mutagenic activity and genotoxic potential. Limited data are available on mutagenicity and genotoxicity of soluble or insoluble Pt compounds. Soluble Pt compounds such as $PtCl_4$ and K_2PtCl_4 have yielded positive results for gene mutation and other genotoxic battery of assays and appear to have mutagenic activity. However, other soluble Pt compounds such as H_2PtCl_6, $[Pt(NH_3)_4]Cl_2$, K_2PtBr_6, and K_2PtCl_6, and insoluble Pt compounds such as $PtCl_2$ have yielded conflicting results from different studies or negative results with no significant mutagenic activity. It is important to note that few studies have been performed for each compound (as few as one study per compound).

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

4.6.1. Oral

Information on the noncancer health effects in humans following acute-, short-term-, subchronic-, or chronic-duration oral exposure to Pt or Pt compounds is limited to a single case report of intentional ingestion of a photographic solution containing 600 mg of potassium chloroplatinite by a 31-year-old man (Woolf and Ebert, 1991). Reported adverse effects include acute oliguric renal failure, metabolic acidosis, fever, muscle cramps, gastroenteritis, and rhabomyolysis. Clinical findings from this single case report suggest that adverse effects on kidney, muscle, and the GI tract are potential outcomes of acute toxicity of potassium chloroplatinite. As discussed below, additional information on the potential nephrotoxicity of Pt compounds is provided in the clinical literature on Pt anticancer agents.

No chronic exposure animal studies have been identified and no 90-day studies have been reported that have comprehensively examined histopathological, biochemical, and clinical endpoints of oral exposure to Pt or Pt compounds. Available studies identify the kidney as a target organ for soluble and insoluble Pt compounds, although the available information is insufficient to fully characterize toxicity outcomes or dose-response relationships. Roshchin et al. (1984) observed epithelial swelling in renal convoluted tubules in rats following acute oral administration of 25 mg/kg fine powder of Pt group metals (Pt and palladium; 1–5 μm diameter); however, it is unclear if the swelling was associated with one or the other metals, or both. Although additional data on potential renal effects of acute oral exposure are not available, rat intraperitoneal LD_{50} values of 40–50 mg/kg for hexachloroplatinic acid were associated with death due to renal failure and necrotizing renal tubular lesions throughout the renal cortex (Ward et al., 1976). In short-term exposure studies, relative kidney weight was significantly increased by 8% in rats exposed to 1.63 mM $PtCl_4$ in drinking water for 29 days (approximately 44.1 mg Pt/kg-day), but no effects on kidney weight were observed in rats exposed to 0.54 mM $PtCl_4$ in drinking water for up to 29 days (reported data inadequate to estimate daily dose) or to 1.63 mM $Pt(SO_4)_2$ in drinking water for 8–9 days (reported data inadequate to estimate daily dose; Holbrook et al., 1975). Decreased renal function, as indicated by increased plasma creatinine concentration, was observed in rats exposed to 50 mg Pt per kg diet as $PtCl_4$ (equivalent to approximately 6 mg Pt/kg-day) for 4 weeks; no information regarding other measures of renal function or potential histopathological changes to the kidney were reported (Reichlmayr-Lais et al., 1992).

The above observations of outcomes indicative of nephrotoxicity are consistent with toxicokinetic studies on soluble and insoluble environmentally relevant Pt compounds and the clinical literature on Pt anticancer agents. Results of toxicokinetic studies in experimental animals show that the highest tissue concentration is reached in the kidney following oral exposure to soluble [$Pt(SO_4)_2$ and $PtCl_4$] or insoluble [$PtCl_2$ and Pt metal] Pt compounds (Artelt

et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975) (Section 3.2.1).

Other adverse effects reported for acute and subchronic oral exposure to environmentally relevant Pt compounds include decreased activity (exploration and rearing) (Lown et al., 1980), hypokinesia, piloerection, diarrhea, convulsions, labored respiration, cyanosis (Degussa, 1989, as cited in WHO, 1991), reduced body weight gain (Holbrook et al., 1975), decreased prothrombin time (magnitude of response not reported) (Roshchin et al., 1984), increased as well as decreased serum levels of urea, and decreased β-lipoproteins (magnitude of response not reported) (Roshchin et al., 1984). However, these effects are nonspecific and do not lead to the identification of other potential target organs. Available information on endpoints other than hypersensitivity is insufficient to evaluate whether the acute and subchronic oral toxicity profiles (e.g., effects or potency) differ between soluble and insoluble Pt compounds.

No studies investigating the reproductive effects of oral exposure to Pt or Pt compounds in experimental animals were identified. The available developmental studies are inadequate to characterize potential effects since dams were not exposed for the entire gestational period and comprehensive developmental endpoints (e.g., external, skeletal, or visceral malformations) were not examined (D'Agostino et al., 1984; Massaro et al., 1981). However, based on a reduction in fetal weight and reduced neonate activity, results indicate that oral exposure of mice to $Pt(SO_4)_2$ is toxic to the developing fetus. Insufficient information is available to describe a dose-response relationship.

4.6.2. Inhalation

4.6.2.1. *Sensitization Effects*

Allergic sensitization to Pt compounds has long been recognized as an occupational hazard for halogenated Pt salts and was first reported in photographic studio workers by Karasek and Karasek (1911). As reviewed previously (Section 4.1.2, *Studies in Humans—Epidemiology, Case Reports, and Clinical Controls, Inhalation*), numerous case reports and epidemiological studies demonstrate that occupational exposure to Pt compounds produces allergic sensitization in some subjects. Evidence suggests that halogenated Pt salts are responsible for allergic sensitization rather than insoluble forms of Pt, although data are not always available to identify individual Pt compounds. Effects associated with allergic sensitization, have been reported in workers exposed to Pt in several types of work environments, including photographic studios (halogenated Pt salts), anode production (applying halogenated Pt salts by brush to anodes), refinement of Pt (halogenated Pt salts), and production of Pt catalysts (involving halogenated Pt salts).

WHO (2000) lists the following range of effects following occupational exposure to halogenated Pt salts: allergic asthma (an inflammatory disorder of the airways that results in shortness of breath), rhinitis (runny nose and sneezing), cough, wheeze, dyspnoea (or difficulty

breathing) and cyanosis (bluish skin due to insufficient oxygen in blood) characteristic of severe asthma, watering of the eyes, itching, urticaria (swollen itching skin), and contact dermatitis (itching skin eruptions). Among the various effects characteristic of Pt-specific allergic sensitization, five main effects (asthma, rhinitis, conjunctivitis, urticaria, and dermatitis) are reported in numerous studies that identify health effects in workers exposed to halogenated Pt salts (Cristaudo et al., 2005; WHO, 2000, 1991; Merget, 2000; Merget et al., 2000, 1999, 1988; Calverley et al., 1999, 1995; Bolm-Audorff et al., 1992; Baker et al., 1990; Pepys, 1984; Pepys et al., 1972; Marshall, 1952; Hunter et al., 1945).

Individuals with halogenated Pt-salt allergic sensitization show progression to moderate or severe asthma with continued exposure (Merget et al., 1999). For halogenated Pt salts and other sensitizers, effects of work-related allergic sensitization may be severe and disabling (Friedman-Jimenez et al., 2000). Severe cases of allergic sensitization to halogenated Pt salts include workers with bluish skin due to insufficient oxygen in blood, feeble pulse, and extreme difficulty breathing requiring the subject to remain upright to breath (Roberts, 1951). Halogenated Pt salt allergy is characterized by exposure followed by a symptom-free latency period typically lasting from 1 month to several years, followed by development of allergic respiratory signs and symptoms (Merget et al., 2000, 1988; Raulf-Heimsoth et al., 2000). However, latency periods less than 1 month have also been reported; a latency period of 1 week was reported in an abstract by Dally et al. (1980), and a 17-day latency period was reported by Pepys et al. (1979). Diagnosis has been based on work-related symptoms, documentation of disease (e.g., asthma, rhinitis), and evidence of sensitization as determined by a SPT to various chlorinated Pt compounds (Merget, 2000). Data on the health effects of chronic Pt exposure in workers following the development of Pt allergic sensitization are complicated by the practice of medically terminating or transferring workers to areas with lower Pt exposure (e.g., Merget et al., 2001, 2000; Calverley et al., 1995; Brooks et al., 1990). Although no deaths have been reported for Pt-specific allergic sensitization, two cases of occupational asthma leading to death have been reported after medical recommendations to permanently cease exposure to other low molecular weight sensitizers (isocyanates) had been given but not followed (Friedman-Jimenez et al., 2000). Even following the work practice of medical termination, about 50% of workers with allergic sensitization to halogenated Pt salts continue to experience symptoms such as asthma and shortness of breath on exertion several years after removal from exposure (Merget et al., 1999, 1994). As discussed in Section 4.6.3.1 (*Mode of Action Information, Sensitization*), Pt sensitization appears to be primarily a Type I (IgE-mediated) hypersensitivity response with some evidence of a second, non-IgE-mediated, mechanism (see discussion of the *Utility of the SPT as an endpoint* in Section 4.6.3.1.4).

Numerous epidemiology studies and case reports indicate that allergic sensitization is caused by halogenated Pt salts, although speciation, characterization, and measurement of the Pt compounds involved are generally not available. Allergic sensitization is well established as a

human health hazard from occupational exposure to airborne halogenated Pt compounds (WHO, 2000, 1991). Several epidemiologic studies have found increased prevalences of workers with allergic sensitization in chloroplatinate-contaminated workplaces with estimated air concentrations <2 μg soluble Pt/m^3 (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). Reported air concentrations of soluble Pt compounds associated with cases of halogenated Pt salt allergy are summarized in Table 4-12. The Bolm-Audorff et al. (1992) study did not include sufficient detail in the exposure measurements to estimate air concentrations for the three exposure categories in the study. The Linnett and Hughes (1999) study did not characterize the Pt exposure beyond soluble Pt. Although no Pt speciation data were provided to substantiate the form of Pt present, Linnet and Hughes (1999) divided worker exposure into three categories by workspace: chloroplatinates alone, mixed exposure to chloroplatinates and tetraamine Pt dichloride, and tetraamine Pt dichloride alone. No information is provided regarding the chemical species present or further characterization of Pt beyond the soluble Pt reported in Merget et al. (2000) or the Pt salt in Baker et al. (1990) that is presented as soluble under the assumption that Pt salt concentrations reported were soluble Pt. See Section 4.1.2.1.2, *Toxicity of Soluble Forms of Pt: Epidemiologic Evidence of Pt Allergic Sensitization*, for more detailed study descriptions.

Table 4-12. Summary of human epidemiology studies of allergic sensitization to Pt

Reference	Study description	Outcomes		
Baker et al., 1990	**Design**: cross-sectional **Subjects**: current workers (n = 107, 92% male) at a precious metals secondary refinery and former workers (n = 29) who were terminated from work because of respiratory tract symptoms between the period 1971–1979 **Outcome measure**: SPT (Na_2PtCl_6) **Exposures**: stationary air monitors (8-hr TWA, collected 1977–1979; method and LOD not reported); exposure measurements not reported for all work areas (e.g., stores)	Prevalence was 0 and 11% in areas that had air concentrations of soluble Pt of 0.6 or 0.4 μg/m^3, respectively, and combined sensitization data were reported for some areas that do not distinguish which exposure data applies to members of that combined group:		
		Work area	**Air (GM) (μg soluble Pt/m^3)**	**Prevalence of sensitization**
		Refinery, tray area	27.1	2/3 (67%)
		Refinery	10.7	2/14 (14%)
		Warehouse	8.6	1/3 (33%)
		Stores	ND	
		Recovery	5.3	1/15 (7%)
		Recovery, sampling	2.7	
		Residue	0.5	
		Manager/office	0.6	0/15 (0%)
		Analytical laboratories	0.4	2/19 (11%)
Linnett and Hughes, 1999	**Design**: retrospective **Subjects**: workers (CPOs) at a precious metal secondary refinery (n = 340, 96% male) employed during the period 1976–1995 **Outcome measure**: SPT (Na_2PtCl_6, $[NH_4]_2PtCl_6$, Na_2PtCl_4, $[Pt(NH_3)_4]Cl_2$) (compounds used in the SPT differed by year) **Exposures**: personal air monitors, analyzed for Pt by electrothermal AAS (LOD not reported), collected 1989–1991	Prevalence was 51% in areas that had air concentrations of soluble Pt <0.5 μg/m^3 in 88% of personal air samples (335/380 sampled 1989–1991):		
		Work area/Pt exposure	**Air (μg soluble Pt/m^3)**	**Prevalence of sensitization**
		PGM refinery/H_2PtCl_6	<0.5 (88%) >2 (2%)	106/170 (51%)
		tetraamine Pt dichloride laboratory/H_2PtCl_6,$[Pt(NH_3)_4]Cl_2$	<0.5 (52%) >2 (28%)	5/31 (16%)
		Catalyst production/$[Pt(NH_3)_4]Cl_2$	<0.5 (61%)	0/39 (0%)
Merget et al., 2000	**Design**: prospective **Subjects**: workers precious metal refinery (n = 275, 96% male) employed during the period 1989–1995 **Outcome measure**: SPT (H_2PtCl_6) **Exposures**: Stationary air monitors (median 12–17 hr TWA) or personal air samples (TWA), analyzed for Pt by ICP-MS (LOD 0.025 ng soluble Pt/m^3) or AAS (LOD 0.13 ng soluble Pt/m^3) collected in 1992 and 1993	Prevalence was 11% in high-exposure group that had median air concentrations of soluble Pt of 0.177 μg/m^3 (personal, sampled 1993) and 0.014 μg/m^3 (stationary, sampled 1992–1993):		
		Exposure category	**Air (median) (μg soluble Pt/m^3)**	**Prevalence of sensitization**
		High	0.014 -0.037 (stationary) 0.177 (personal)	13/115 (11%)
		Low	0.0004–0.0066 (stationary)	0/111 (0%)
		No exposure	0.00005	0/48 (0%)

AAS = atomic absorption spectrometry; CPO = chemical process operator; GM = geometric mean; ICP-MS = inductively coupled plasma/mass spectrometry; LOD = limit of detection; PGM = platinum group metals; TWA = time weighted average

The allergenic activity of halogenated Pt salts is supported by three inhalation exposure studies in primates and a larger number of dermal and parenteral exposure studies in experimental animals. The results of the three available animal studies of inhalation exposure to Pt (Biagini et al., 1986, 1985b, 1983) support the possibility that co-exposure to ozone may promote the development of allergic sensitization to halogenated Pt salts. As reviewed in Section 4.5.1 (*Sensitization Studies*), Biagini et al. (1986) reported sensitization in 1/8 monkeys following subchronic exposure to inhaled hexachloroplatinate alone and in 4/8 monkeys exposed to hexachloroplatinate plus ozone, compared to 0/7 in those receiving ozone alone. Studies assessing the potential sensitizing effects of inhaled hexachloroplatinate in monkeys were conducted in a small number of animals, thus limiting the power to detect sensitization. Furthermore, the length of the latency period to develop sensitization to hexachloroplatinate in monkeys has not been determined; therefore, it is unclear how the exposure duration may have affected response rate. However, even with these limitations, Biagini et al. (1986) detected sensitization in 1/8 monkeys exposed to hexachloroplatinate by inhalation for 12 weeks. A low response rate is consistent with the characteristics of a Type I allergic response in humans, in which only a fraction of exposed individuals are expected to become sensitized (see Section 4.6.3.1, *Mode of Action Information, Sensitization*). Dermal application of hexachloroplatinate to mice induced dermal hypersensitivity and a lymphocyte secretion profile of cytokines consistent with an allergic response (Dearman et al., 1998; Schuppe et al., 1997a) and parenteral exposure of rats and mice to hexachloroplatinate induced sensitization (Schuppe et al., 1997b, 1992; Murdoch and Pepys, 1986, 1985, 1984a, b). Results of the Schuppe et al. (1997b) study in mice and the Murdoch and Pepys (1985, 1984b) studies in rats showing that tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) did not exhibit immunogenic activity are consistent with results of the epidemiology study by Linnett and Hughes (1999) showing that no cases of sensitization were observed among 39 workers exposed to $[Pt(NH_3)_4]Cl_2$ in the production of automotive catalysts. Similar results were reported by Steinfort et al. (2008) in a prospective study of workers at a catalyst manufacture plant in Melbourne, Australia, where no cases of positive SPT were reported among workers with reported exposure to $[Pt(NH_3)_4]Cl_2$. However, the Linnett and Hughes (1999) and Steinfort et al. (2008) studies does not include exposure data on the particular Pt compounds to which workers are exposed and workers are instead classified by work area without speciated Pt exposure data. Although available data are inadequate to characterize the exposure level-response relationship for induction of halogenated Pt salt allergy in animals exposed by inhalation, results provide evidence to support the numerous reports of allergic sensitization to halogenated Pt salts in groups of occupationally exposed workers.

The allergenic activity of Pt is compound-dependent, since sensitization effects appear to be restricted to the halogenated Pt salts and there is no evidence of allergic sensitization following exposure to insoluble Pt compounds. Data suggest that sensitization to the halogenated Pt salts may be related to the halogen-ligands coordinated to Pt and the negative

charge of these complexes (Nischwitz et al., 2004; Ravindra et al., 2004; Rosner and Merget, 2000; Cleare et al., 1976). The reactivity of these Pt coordinated halogen-ligands with proteins is important in the generation of Pt-specific immune response because low molecular weight chemicals such as Pt must act as haptens by binding with larger endogenous substances before they can generate an allergic response (see Sections 4.6.3.1.1–3 for a detailed description of haptens and the Type I allergic response). Support for the importance of this reactivity of Pt coordinated halogen-ligands is provided by evidence that suggests tetraamine Pt dichloride may not cause Pt-specific allergic sensitization. Results of the retrospective occupational exposure study by Linnett and Hughes (1999) show that exposure to tetraamine Pt dichloride alone was not associated with sensitization in workers, whereas mixed exposure to tetraamine Pt dichloride and halogenated Pt salts (chloroplatinates) was associated with allergic sensitization. Halide is present as an ion in tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) and not a ligand coordinated to Pt; therefore, $[Pt(NH_3)_4]Cl_2$ is a halogenated complex, not a halogenated Pt salt (Linnett and Hughes, 1999; Cleare et al., 1976). The Pt in $[Pt(NH_3)_4]Cl_2$ is bonded to nitrogen and ligand substitution necessary to react with proteins is extremely slow and may not take place on a biologically relevant timescale (Cleare et al., 1976). SPT results in sensitized Pt refinery workers showed that activity in the SPT, or inflammation in individuals already sensitized to halogenated Pt salts, was directly related to the number of chlorine atoms in a series of halogenated Pt salts, with the highest activity (i.e., IgE-mediated inflammation) associated with ammonium hexachloroplatinate and ammonium tetrachloroplatinate (Cleare et al., 1976). Several soluble Pt compounds that were not halogenated Pt salts, including tetraamine Pt dichloride, yielded negative SPT results. Results of the Schuppe et al. (1997b) study in mice and the Murdoch and Pepys (1985, 1984b) studies in rats showing that tetraamine Pt dichloride did not exhibit immunogenic activity provide supporting evidence for the findings of Linnett and Hughes (1999) and Cleare et al. (1976). Tetraamine Pt dichloride doesn't show any strong evidence of being a sensitizer. Data from Cleare et al. (1976) also show that non-halogenated soluble Pt compounds such as $K_2Pt(NO_2)_4$ were negative in the SPT. Limited evidence also supports the lack of allergenic potential of insoluble Pt compounds. Hunter et al. (1945) reported that occupational asthma was not observed in workers primarily exposed through processes that involved very heavy exposure to airborne, insoluble, Pt metal. Furthermore, results of the in vitro study by Di Gioacchino et al. (2004) indicate that insoluble $PtCl_2$ did not have immune effects (proliferation or cytokine release from on isolated human PBMCs), whereas soluble halogenated Pt salts demonstrated immune activity in this model.

4.6.2.2. *Other Adverse Effects (Respiratory Irritation, Nephrotoxicity, Neurotoxicity, Ototoxicity)*

Respiratory Irritation. Inhalation exposure to insoluble Pt compounds has the potential to produce respiratory irritation and/or inflammation. Respiratory irritant or inflammatory

activity from chronic inhalation exposure to insoluble Pt forms is supported by the following observations: (1) pulmonary inflammation in aged emphysematous rats acutely exposed to ultrafine Pt particles (Oberdörster, 2001), and (2) a correlation between Pt concentrations in nasal lavage fluid and markers of nasal inflammation (increased neutrophils and epithelial cells) in a group of children (Schins et al., 2004). Although the Schins et al. (2004) study supports the potential for Pt to produce respiratory irritation or inflammation, a link between concentrations in the nasal lavage fluid and air concentrations of Pt was not demonstrated, and corroborative findings of the correlation between Pt concentrations in nasal lavage fluid and increased markers of nasal inflammation are not available.

Acute exposure to halogenated Pt salts has been shown to produce direct effects on the airway. Using a primate animal model, Biagini et al. (1985b) reported that acute inhalation exposure to Na_2PtCl_6 altered pulmonary function, producing peripheral and central airway constriction (see Section 4.4.2 for complete study details). Since this study was performed in animals with no prior exposure to Na_2PtCl_6 or any other Pt compound, results provide evidence that Na_2PtCl_6 can produce direct effects on the airway in the absence of IgE-mediated sensitization to Pt. Furthermore, the authors conclude that the response was not indicative of irritation because respiratory rate was not affected by treatment.

Nephrotoxicity, Neurotoxicity, and Ototoxicity. As summarized in Section 4.6.1. (*Synthesis of Major Noncancer Effects, Oral*), oral exposure of animals to soluble and insoluble Pt compounds and the clinical experience with Pt anticancer drugs identify the kidney as a potential target organ for toxicity of Pt compounds. Other adverse effects commonly associated with parenteral administration of Pt anticancer drug include neurotoxicity and ototoxicity (see Section 4.4.3, *Drug Studies*). However, occupational exposure studies and case reports do not identify nephrotoxicity, neurotoxicity, or ototoxicity as adverse effects of inhalation exposure to soluble or insoluble Pt compounds. Furthermore, no evidence for effects (other than sensitization) was reported in short-term inhalation studies in animals, although comprehensive toxicity endpoints (e.g., gross pathology, histopathology, biochemistry, hematology, signs of toxicity) were not evaluated and no routine 90-day or chronic toxicity studies of soluble or insoluble Pt compounds are available other than studies of the Pt anticancer drugs discussed in Section 4.4.3.

4.6.3. Mode of Action Information

4.6.3.1. *Sensitization*

4.6.3.1.1. ***Type I allergic responses.*** The symptoms and time-course of the hypersensitivity response to halogenated Pt salts are typical of an IgE-mediated, Type I allergic reaction. However, the possibility that a second, non-IgE-mediated mechanism, is responsible for some cases of allergic sensitization to halogenated Pt salts is suggested by several lines of evidence including pulmonary effects of Pt compounds in naive monkeys (Biagini et al., 1985b) and the

failure of skin prick testing to identify all workers displaying symptoms of allergic sensitization to halogenated Pt salts (see Section 4.6.3.1.4 *Utility of the SPT as an endpoint* for further discussion of non-Type I mechanisms). Although immune-mediated hypersensitivity reactions are not completely understood, the following general scheme of Type I reactions is well accepted (Descotes, 2004; Goldsby et al., 2003b). Upon initial contact with an allergen, B lymphocytes produce specific antibodies, probably of the IgG isotype. The B lymphocytes undergo class switching to produce IgE antibodies of the same specificity. Antibodies of the IgE isotype can bind to high affinity receptors on membrane surfaces of mast cells and basophils through the Fc portion of the antibody. Mast cells and basophils with membrane-bound IgE are considered to be sensitized. Upon subsequent exposure to the same antigen, although not necessarily the next exposure, antigen binds to the Fab portion of the antibody on sensitized cells, triggering cellular degranulation. Symptoms of Type I hypersensitivity reactions (e.g., asthma, rhinitis, urticaria, conjunctivitis, dermatitis, and anaphylaxis) are caused by degranulation products, including histamine, leukotrienes, prostaglandins, and proteases, and may be localized or systemic, depending upon the extent of mediator release. Since the mediators released by degranulation act quickly to produce effects, Type I allergic reactions are termed "immediate hypersensitivity reactions", even though the symptom-free latency period after initial antigen exposure may last for several years.

Type I hypersensitivity reactions can be diagnosed through skin prick testing or determination of serum levels of Pt antigen-specific IgE by RAST testing. Detailed information on the use of the SPT in the diagnosis of Type I hypersensitivity reactions to Pt compounds is provided in Section 4.1.2.1.1 (*Toxicity of soluble forms of Pt: diagnosis of Pt allergic sensitization*) and Section 4.6.3.1.4 (*Utility of the SPT as an endpoint to identify Pt-specific sensitization*). The RAST test appears to be less sensitive than the SPT in the clinical diagnosis of Pt IgE-mediated allergy. Due to the high affinity of Pt compounds to IgE antibodies, a high degree of non-specific binding interferes with detection of Pt-specific antibodies (Merget, 2000; Biagini et al., 1985a). Thus, although Pt-specific IgE antibodies have been identified by RAST analysis in skin test positive workers (Murdoch et al., 1986; Biagini et al., 1985a; Cromwell et al., 1979), RAST test results are not considered sensitive enough for individual diagnosis of IgE-mediated hypersensitivity to Pt compounds.

Symptoms of allergic sensitization (asthma, rhinitis, conjunctivitis, urticaria, and dermatitis) and the time-to-onset of effects (e.g., symptom-free latency period) in exposed workers are consistent with the effects and time-course observed for a Type I allergic reaction (Section 4.1.2, *Studies in Humans—Epidemiology, Case Reports, Clinical Controls—Inhalation*).

The clinical presentation of halogenated Pt salt sensitization meets the following criteria for a Type I allergic response: (1) symptoms occur only after a symptom-free latency period; (2) only a fraction of exposed subjects become sensitized; (3) sensitivity increases over time and sensitized individuals react to low exposure levels; and (4) SPTs using halogenated Pt salts (e.g.,

$[NH_4]_2PtCl_6$ and Na_2PtCl_6) as the test chemical on atopic and non atopic controls yield negative results (WHO, 1991; Rosner and Merget, 1990).

(1) *Symptoms occur only after a symptom-free latency period*: Data from the occupational studies suggests that sensitization can develop over an exposure period of several months to over 13 years (Cristaudo et al., 2005; Merget et al., 2000; Raulf-Heimsoth et al., 2000; Linnet and Hughes, 1999; Bolm-Audorff et al., 1992; Merget et al., 1988). Merget (2000) states that most cases of allergic sensitization to halogenated Pt salts develop within several years of exposure. However, latency periods less than 1 month have also been reported; a latency period of 1 week was reported in an abstract by Dally et al. (1980), and a 17-day latency period was reported by Pepys et al. (1979).

(2) *Only a fraction of exposed subjects become sensitized*: Early occupational studies of allergic sensitization to halogenated Pt salts in Pt refineries report prevalence of sensitization as high as 57% (Hunter et al., 1945) and 73% (Roberts, 1951) based on symptoms of sensitization. More recent studies that used positive SPT to halogenated Pt-salts to determine sensitization to halogenated Pt-salts have reported sensitization prevalences between 12.4 and 38.5% (Brooks et al., 1990 reported 14% in a U.S. refinery; Murdoch et al., 1986 reported 12.4% in a South African refinery; Merget et al., 1988 reported 38.5% in a German refinery; Bolm-Audorff et al., 1992 reported 18.7% in a German refinery).

(3) *Sensitivity increases over time and sensitized individuals react to low exposure levels*: Data on the health effects of chronic Pt exposure in workers following the development of Pt allergic sensitization and the potential for increased sensitivity over time is complicated by the practice of medically terminating or transferring workers to areas with lower Pt exposure (e.g., Merget et al., 2001, 2000; Calverley et al., 1995; Brooks et al., 1990). Individuals with halogenated Pt-salt allergic sensitization show a progression of symptom severe asthma with continued exposure (Merget et al., 1999; Hunter et al., 1945). Most occupational studies show that sensitized individuals react to low exposure levels and the results of the SPT provide the best quantitative data of the increased sensitivity of workers sensitized to halogenated Pt salts. Brooks et al. (1990) reported positive SPT to halogenated Pt salts in sensitized workers at concentrations as low as 10^{-8} g/mL. Merget et al. (1991) report positive specific bronchial provocation tests with halogenated Pt salts as low as 10^{-6} mol/L (10^{-8} g/mL).

(4) *SPTs using halogenated Pt salts (e.g., $[NH_4]_2PtCl_6$ and Na_2PtCl_6) as the test chemical on atopic and non atopic controls yield negative results*: The SPT to halogenated Pt salts is commonly performed at concentrations in the range of 10^{-3} g/mL (e.g., SPT were performed to $[NH_4]_2PtCl_6$, Na_2PtCl_6, and Na_2PtCl_4 at 10^{-3} g/mL in Linnett and Hughes, 1999 and to H_2PtCl_6 at 4.1×10^{-3} g/mL and Merget et al., 2000). At that concentration (i.e., 10^{-3} g/mL) control subjects are negative in SPT to halogenated Pt salts. Atopics without occupational exposure to halogenated Pt salts are negative in the SPT and false positive SPTs are generally not reported as the test is very specific for halogenated Pt salt allergy (Merget et al., 1991; reviewed in Merget, 1990). In Books et al. (1990), one of the few studies to test a range of concentrations for the SPT, control subjects were negative at test concentrations ranging from 10^{-9} to 10^{-3} g/mL, with the exception of a biologic scientist that had previously worked extensively with Pt salts.

Individuals with halogenated Pt-salt allergic sensitization showed progression to moderate or severe asthma with continued exposure (Merget et al., 1999). For halogenated Pt salts and other sensitizers, effects of work-related allergic sensitization may be severe and disabling (Friedman-Jimenez et al., 2000). Severe cases of allergic sensitization to halogenated Pt salts included workers with bluish skin due to insufficient oxygen in blood, feeble pulse, and extreme difficulty breathing requiring the subject to remain upright to breath (Roberts, 1951). Although no deaths have been reported for Pt-specific allergic sensitization, two cases of occupational asthma leading to death were reported after medical recommendations to permanently cease exposure to other low molecular weight sensitizers (isocyanates) had been given but not followed (Friedman-Jimenez et al., 2000). Even following the work practice of medical termination, about 50% of workers with allergic sensitization to halogenated Pt salts continued to experience symptoms such as asthma and shortness of breath on exertion several years after removal from exposure (Merget et al., 1999, 1994).

Several occupational exposure studies provide data strongly supportive of an IgE-mediated mode of action for sensitization effects of halogenated Pt salts. An association between elevated total serum IgE levels and sensitization has been reported in exposed workers (Merget et al., 1988; Murdoch and Pepys, 1987; Murdoch et al., 1986; Biagini et al., 1985a). Merget et al. (2000) reported an association between SPTC and total IgE ($p = 0.036$); however, the authors reported that total IgE did not differ between exposure categories. In workers removed from exposure, total serum IgE levels were significantly reduced (Merget et al., 1999, 1994). Although attempts to identify Pt-specific IgE antibodies by RAST analysis have not yielded consistent results, possibly due to interference from nonspecific reactions of Pt halide complexes with immunoglobulins (Merget et al., 2000; Cleare et al., 1976), Pt-specific IgE antibodies have been identified by RAST analysis in skin test positive workers (Murdoch et al., 1986; Biagini et al., 1985a; Cromwell et al., 1979). The existence of Pt-specific antibodies is also supported through passive transfer of skin test reactivity; positive SPT reactions were observed in both humans and monkeys using sera from sensitized workers (Pepys et al., 1979; Freedman and Krupey, 1968). Taken together, results of occupational exposure studies strongly indicate that sensitization effects for halogenated Pt salts are generally mediated through an IgE-mediated mode of action.

4.6.3.1.2. ***Type II, Type III, and Type IV allergic responses.*** An additional IgG-mediated mechanism may be involved in the development of halogenated Pt salt allergy, as proposed by Pepys et al. (1979) (study details are provided in Section 4.5.1.1.2). IgG-mediated hypersensitivity reactions are classified as Type II or Type III. In Type II hypersensitivity reactions, IgG or IgM antibodies are produced in response to antigens bound to cells. Type II reactions can be intrinsic (e.g., the antigen is a cell-attached endogenous substance) or extrinsic (e.g., the antigen is a foreign body adsorbed onto a cell). The IgG or IgM antibodies bind to

these antigens, initiating an inflammatory response and other events leading to cell lysis and death (Goldsby, et al., 2003a). In Type III hypersensitivity, the antigen and antibody (IgG or IgM) form a soluble immune complex (aggregations of antigens and IgG and IgM antibodies) in the blood. The antibody-antigen complexes are then deposited in various tissues (typically, skin, kidney, and joints), resulting in a reaction at the sites of antibody-antigen complex deposition (Goldsby et al., 2003a).

Unlike the preceding three types, Type IV reactions are mediated by activated T cells rather than antibodies. Much has been learned about T cells since the four hypersensitivity classifications were originally proposed. As a result, the Type IV responses can now be divided into three subtypes, mediated by different populations of T cells, $CD4^+$ T helper (Th)1 and Th2 cells, and $CD8^+$ cells (Janeway et al., 2005). These $CD4^+$ cells recognize modified extracellular proteins presented in the context of MHC-II molecules and activate macrophages, which release a variety of cytokines and chemokines, leading to inflammation characterized by the influx of neutrophils. $CD8^+$ T cells are cytotoxic and attack cells bearing modified intracellular proteins that are presented on the cell surface in the context of MHC-I antigens. Th1 and CD-8 reactions generally occur 24–48 hours after exposure in a previously sensitized individual and are thus referred to as delayed-type hypersensitivity. Hypersensitivity pneumonitis includes both Th1 and CD-8 responses (Greenberger, 2008). Th2 cells facilitate the antibody class switch to IgE and mobilize and activate eosinophils and mast cells. Chronic responses in allergic asthma are, in part, attributable to Th2 cells.

4.6.3.1.3. ***Low molecular weight chemicals such as Pt act as haptens to produce sensitization.*** For low molecular weight chemicals (<1,000 kDa), such as halogenated Pt salts, to induce a hypersensitivity reaction, the chemical must act as a hapten, binding to a large molecular weight endogenous substance to form an antigenic complex (Rosner and Merget, 1990). Unlike conventional protein allergens (e.g., dust-mites), low molecular weight chemicals are too small by themselves to be recognized by the immune system as foreign and are therefore too small to elicit an allergic response without forming a complex with a larger molecule. The probability that a given low molecular weight chemical would be a sensitizer depends on the reactivity of the chemical. A given chemical must be reactive enough to complex with larger molecules, usually host proteins, to be a sensitizer. This chemical-protein complex is then recognized by the immune system, which may result in the generation of hapten-specific immune responses (Sarlo and Clark, 1992).

Low molecular weight chemical sensitizers are typically electrophiles, or proelectrophiles, capable of reacting with hydroxyl, amino, and thiol groups on proteins (Karol et al., 2001). The reactivity of chemical sensitizers may also contribute to allergenicity by cross-linking individual proteins and forming new epitopes. For well-studied low molecular weight chemicals, such as the isocyanates, data indicate that chemicals become conjugated to serum

albumin, glutathione, and other proteins of the airway and skin epithelium upon inhalation (Karol et al., 2001; Wisnewski et al., 2001). The specific protein or proteins responsible for haptenization of halogenated Pt salts in humans is not known. In animals studies, OVA was successful in forming an allergen when conjugated to ammonium tetrachloroplatinate ($[NH_4]_2PtCl_4$) as evidenced by positive specific RAST against the Pt moiety when rats were challenged to $(NH_4)_2PtCl_4$ conjugated to OVA (Murdoch and Pepys, 1984b). This contrasts to the failure of free $(NH_4)_2PtCl_4$ to induce Pt-specific IgE following immunization via intraperitoneal, intramuscular, intradermal, intravenous, intratracheal, or footpad challenge under the same conditions, even in the presence of adjuvants.

Consistent with current scientific knowledge of allergenicity of low molecular weight chemicals, Cleare et al. (1976) hypothesized that the strength of the Pt ligand bond and the reactivity of the Pt compound with endogenous proteins play a significant role the determining the allergic potential of Pt compounds. Linnett and Hughes (1999) hypothesized that, in humans, the most likely site of the Pt chemical-protein bond would be to the sulfur in methionine groups on HSA. Furthermore, the authors identify the chloride ions in chloroplatinate as comparatively labile leaving groups that allow substitution by sulfur- or nitrogen-containing ligands to occur on a biologically relevant time scale. By contrast, the authors suggest that substitution in tetraamine Pt dichloride is extremely slow and formation of a Pt-protein complex with this compound would be reduced and may not form under normal occupational exposure (Linnet and Hughes, 1999).

4.6.3.1.4. ***Utility of the SPT as an endpoint to identify Pt-specific sensitization.*** SPTs are routinely used in the diagnosis of sensitization to halogenated Pt salts in conjunction with work-related symptoms of allergy, pulmonary function tests, and specific and nonspecific bronchial challenge tests. As discussed in detail in Section 4.1.2.1.1 (*Toxicity of soluble forms of Pt: diagnosis of Pt allergic sensitization*), SPTs detect only Type I, IgE-mediated sensitization. Since most cases of allergic sensitivity to Pt are thought to be due to IgE-mediated immune mechanisms (see Section 4.6.3.1, *Mode of Action Information, Sensitization*), sensitivity to specific Pt compounds can be detected through SPTs in many sensitized individuals. For example, among the 13 cases of workers who developed a positive SPT to Pt in a 5-year prospective study of 115 high-exposure catalyst production workers, all displayed symptoms (rhinitis, asthma, or dermatitis), although the symptoms were not work-related in a few of these cases (Merget et al., 2000). No subject with a negative SPT and new work-related symptoms (n = 6 in the high-exposure group) showed a positive SPT upon follow-up exam (Merget et al., 2000). In a retrospective study of 406 U.K. refinery workers exposed to chloroplatinates, 110 cases of halogenated Pt salt allergy were identified; of these, 100 were SPT positive (Linnett and Hughes, 1999). Among the 10 SPT-negative cases, 1 was positive in a patch test, 1 was positive in a specific bronchial challenge test, 1 had work-related upper respiratory symptoms, and 7 had bronchospasms at work.

Sensitization would not be detected using the SPT if the response to halogenated Pt salts in a subset of sensitized individuals is mediated through a non-IgE mechanism. Results of a study by Merget et al. (1991) found that Pt SPT does not always predict the respiratory response to hexachloroplatinate (study details provided in Section 4.1.2.1.1). The data support the hypothesis that a non-IgE mechanism may be involved in the respiratory response in some individuals, based on the finding that positive hexachloroplatinate bronchial challenge was observed in a few workers testing negative in the hexachloroplatinate SPT. Similar findings have been reported for other chemicals with known allergic sensitization properties. For example, immunologic respiratory effects have been observed in workers exposed to diisocyanate; however, the association between diisocyanate-specific IgE antibodies and respiratory symptoms appears to be variable or absent (Kimber and Dearman, 2002; Redlich and Karol, 2002; Kimber et al., 1998). Furthermore, four immunologically-mediated respiratory syndromes (one IgE- mediated and three IgG-mediated) have been identified for the respiratory sensitizer TMA (Grammer et al., 1998). Thus, it is possible that multiple mechanisms are involved in sensitization to hexachloroplatinate or other halogenated Pt salts.

Additional support that at a least a portion the allergic sensitization to Pt is non-IgE-mediated is provided by a study examining the respiratory response of methacholine and Na_2PtCl_6 in naïve (i.e., not previously exposed to Na_2PtCl_6 or other Pt compounds) cynomolgus monkeys (Biagini et al., 1985b). Male monkeys (n = 24) were evaluated for pulmonary responsiveness to inhaled (nebulized) aerosols of methacholine (0, 0.1, 0.5, 1.05, or 6.25 mg/mL in phosphate buffered saline) or Na_2PtCl_6 (0, 0.5, 2.5, 25, or 50 mg/mL in saline). For both test agents, MMADs ranged from 1.0 to 1.5 µm, with GSD s of 1.7–2.0. Bronchial challenges for each dose of methacholine and Na_2PtCl_6 were performed for 1 minute (15 breaths). The study report did not specify how each agent was administered, although bronchoprovocation agents are typically administered using a breathing tube. Monkeys were anesthetized for all challenge tests. Tests were first conducted with methacholine, followed 2–3 weeks later by tests with Na_2PtCl_6 in the same monkeys. The following pulmonary function variables were assessed following exposure to each dose of challenge agent: average pulmonary resistance (R_L); dynamic compliance (C_{Ldyn}); PEFR; FVC, $FEV_{0.5}$/FVC ($FVC_{0.5}$/FVC); FEFs at 50 and 25% of vital capacity normalized for FVC (FEF_{50}/FVC and FEF_{25}/FVC); and respiratory rate. All pulmonary function test results were reported graphically. For measures of airway mechanical status at tidal breathing ($R_L$and C_{Ldyn}), effects of methacholine and Na_2PtCl_6 were similar. Both agents produced dose-dependent increases in R_L, with maximal increases (relative to the pre-challenge response on the test day) at the highest dose tested of approximately 550% for methacholine and almost 700% for Na_2PtCl_6. Both agents also produced dose-dependent decreases in C_{Ldyn}, with a maximal decrease of approximately 50% (for methacholine and Na_2PtCl_6) at the highest challenge dose. Methacholine and Na_2PtCl_6 also produced dose-dependent decreases in airflow in central and peripheral airways under maximal expiratory conditions ($FVC_{0.5}$/FVC and PEFR)

and under conditions of low lung volumes (FEF_{50}/FVC and FEF_{25}/FVC); however, the decreases were significantly greater compared to those observed for methacholine ($p < 0.05$). Since respiratory rate was not affected by either treatment, the study authors concluded that neither challenge agent stimulated respiratory irritant receptors. Results of this study indicate that both methacholine and Na_2PtCl_6 produce peripheral and central airway bronchoconstriction; however, they appear to act, at least in part, through different mechanisms. Furthermore, since this study was performed in animals with no prior exposure to Na_2PtCl_6 or any other Pt compound, results provide evidence that Na_2PtCl_6 can produce airway effects in the absence of IgE-mediated sensitivity to Pt.

Since SPTs detect IgE-mediated sensitization, other factors that may affect circulating levels of IgE antibodies to hexachloroplatinate could potentially affect SPT results. For example, Merget et al. (1994) reported that in a few workers removed from exposure, SPT to hexachloroplatinate converted from positive to negative, although these workers still tested positive in bronchial challenge tests to hexachloroplatinate and methacholine. This finding is consistent with the hypothesis that low circulating levels of Pt-specific IgE antibodies following an exposure-free period may not be sufficient to yield a measurable response to detect sensitization by hexachloroplatinate SPT. For example, in some individuals sensitized to diisocyanate, decreased circulating diisocyanate-specific IgE levels have been observed following an exposure-free period (Kimber and Dearman, 2002; Tee et al., 1998).

4.6.3.1.5. ***Correlation between Pt sensitization and asthma/atopy toward other allergens.*** The data examining the correlation between Pt sensitization and asthma/atopy toward other allergens are limited to a few epidemiologic studies in occupationally exposed workers (Merget et al., 2000; Calverley et al., 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). Some studies have shown equal or reduced sensitivity to environmental allergens in halogenated Pt salt-exposed populations compared to nonexposed controls (e.g., Merget et al., 2000), while others have shown an increase in sensitivity to environmental allergens with Pt-salt exposure (Calverley et al., 1999). The in vitro studies of human dendritic cells by Paolucci et al. (2007) suggest that Na_2PtCl_6, and some palladium and rhodium compounds, may act on dendritic cells in an adjuvant-like way such that exposure results in an increased allergic response to allergens. Occupational data may be confounded by the exclusion of atopic individuals from high-exposure jobs, thereby selecting for reduced sensitivity to the development of allergies or asthma. Common nonspecific irritants such as smoke and diesel exhaust are likely to exacerbate the asthmatic condition, as reflected in reports that both nonspecific and specific bronchial responsiveness persist in a considerable number of sensitized workers after removal from the workplace or from high-exposure workplace areas (Merget et al., 1999, 1994). In a recent review of the epidemiological literature examining the relationship between environmental asthma triggers (e.g., tobacco smoke, outdoor air pollutants, pollen) and asthma incidence,

Gilmour et al. (2006) suggest that complex organic molecules in diesel exhaust may act as allergic adjuvants and exacerbate asthma or increase the likelihood of developing allergic asthma (Gilmour et al., 2006). This hypothesis is supported by results of studies in humans and rodents showing that diesel exhaust particles acted as an adjuvant, enhancing the IgE-mediated response to allergens (ragweed in human subjects—Diaz-Sanchez et al., 1997; OVA in mice Lovik et al., 1997). Diesel exhaust particles also acted as an adjuvant producing an IgE-mediated response in 9/15 subject challenged with diesel exhaust particles and keyhole limpet hemocyanin (KLH), whereas no individuals (0/10) developed anti-KLH-specific IgE when exposed to KLH alone (Diaz-Sanchez et al., 1999). However, the potential for the diesel exhaust to act as an adjuvant and exacerbate asthma in Pt sensitized individuals has not been established.

4.6.3.1.6. ***Relevance of acute versus chronic exposures and of repeated versus single exposures in the development of Pt sensitization.*** The information from the available epidemiologic studies is inadequate to specify the duration of exposure or exposure concentrations necessary to induce halogenated Pt salt allergic sensitization. In the only study from which a NOAEL can be identified for halogenated Pt salt sensitization (Merget et al., 2000), exposure estimates for workers in the high-exposure group (in which 13/115 workers developed halogenated Pt salt sensitization as assayed by SPT during a 5-year period) were highly variable (100- and 1,000-fold variations were reported for stationary air and personal air samples) and individual personal air samples were not collected for each worker in the study. It is unclear from the data whether the development of sensitization was better associated with high concentrations that the workers may have intermittently experienced or with a central tendency measure of air concentrations experienced across the period of occupation. The data provide some information that the workplace conditions may have been sufficient to require less than a "chronic" duration for the development of sensitization; nine of the high-exposure workers became sensitized during year 3 of the study, while the others did so in years 1, 2, 4, and 5 (Merget et al., 2000). However, the high-exposure workers were employed in their jobs for 15–27 months before the initial survey in the study. As discussed in Section 4.6.3.1 (*Mode of Action Information, Sensitization*), a Type I hypersensitivity response requires more than one exposure before symptoms develop. Symptoms may develop after relatively few exposures or may develop after several years of exposure, as reported by Merget et al. (2000). In general, as the sensitization dose of an allergen increases, the dose needed to elicit a response on re-challenge decreases (Hostynek and Maibach, 2004; Scott et al., 2002). However, several factors may affect this relationship, including frequency of exposure, single versus multiple exposures, and biological half-life of the allergen (Scott et al., 2002). A further complication in identifying threshold doses for sensitization and elicitation (e.g., re-challenge) involves the mechanism of sensitization. Studies examining the dose-response relationship for sensitization indicate that humoral responses (e.g., B cell-mediated) are induced in response to high doses, whereas, cell-

mediated responses (e.g., T cell-mediated) are induced with lower doses (Constant and Bottomly, 1997). Given the many factors that may influence the sensitization and elicitation thresholds, coupled with variations in worker exposure, the relationship between the dose of halogenated Pt salts needed to produce sensitization and the dose needed to elicit a response on re-challenge has not been established. The exposure data from Merget et al. (2000) for the high-exposure group identify an occupational exposure concentration associated with sensitization, as 13/115 workers in the high-exposure group developed Pt-specific allergic sensitization as determined by positive SPT during the 5-year study. The dose of hexachloroplatinic acid (4.1 g/L) used for the SPT represents the elicitation dose in this study. A single dose level was used for the elicitation in the SPT; therefore, no information on the dose-response for elicitation is available from Merget et al. (2000).

4.6.3.1.7. ***Relationship between exposure levels associated with sensitization and the subsequent exposure levels required to elicit a response.*** There is little experimental evidence to characterize the relationship between the dose required to induce allergic sensitization (i.e., induction or sensitization dose) via respiratory exposure and the subsequent dose required to elicit the allergic response (i.e., challenge or elicitation dose). However, the elicitation dose is generally lower than the dose required to induce sensitization for both contact and respiratory sensitization (Arts et al., 2006; Rosner and Merget, 2000). The relationship between the dose-response curves for sensitization and elicitation are better studied for dermal exposure in allergic contact dermatitis. There is a clear inverse correlation between the strength of the sensitization and the subsequent dose required to elicit a contact hypersensitivity response in humans (Friedmann, 2007). The strength of sensitization is, in turn, related to the potency of the allergen and the dose that reaches the skin (Friedmann, 2007). The slopes of dose-response relationships for sensitization in the induction of allergic contact dermatitis from certain chemicals have been shown to be similar to the slopes for elicitation dose-response relationships, albeit elicitation curves are shifted to lower ranges of the dose axis (Scott et al., 2002; Friedmann, 1994, 1990).

Studies of the SPT responses in Pt-sensitized individuals indicate that concentrations that elicit a positive reaction are, for many cases, 3 orders of magnitude lower than the maximum SPT concentration which elicits no response in nonsensitized subjects, and that, for rare cases, the difference may be as much as 6 orders of magnitude. For example, in a study of 107 actively employed refinery workers and 30 former workers, Biagini et al. (1985a) reported the following distribution of the elicitation doses required for a positive SPT result[2] among the 23 sensitized

[2] Note the concentration reported is the lowest concentration associated with a positive SPT to $(NH_4)_2PtCl_6$.

individuals: 10^{-3} g/mL (n = 2); 10^{-4} g/mL (n = 3); 10^{-5} g/mL (n = 4); 10^{-6} g/mL (n = 9); 10^{-7} g/mL (n = 3); 10^{-8} g/mL (n = 1); and 10^{-9} g/mL (n = 1). The elicitation doses ranged from 10^{-9} to 10^{-3} g/mL.

4.6.3.1.8. ***Cross-sensitivity between Pt and other metals for sensitization.*** No data were located to describe the structure-activity relationship between Pt and other Pt group metals (i.e., palladium, ruthenium, rhodium, osmium, iridium, and Pt). Studies in rats (Murdoch and Pepys, 1985, 1984a, b; study details provided in Section 4.5.1.1.2) indicate that OVA-Pt specific IgE-antibodies are not cross-reactive to chlorinated salts of other PGEs. On the other hand, several occupational studies demonstrate sensitization to other PGEs in humans that have a known allergic sensitization to halogenated Pt salts (Cristaudo et al., 2005; Murdoch and Pepys, 1987; Murdoch et al., 1986). A similar sensitization to halogenated Pt salts and other PGEs (Pt and palladium) as well as gold (gold sodiumthiosulfate) was observed in a analytical chemist testing various metal plating solutions (Watsky, 2007).

In occupational situations (including Pt refineries and catalyst production and recycling facilities) where exposure to halogenated Pt salts takes place with co-exposure to halogenated salts of other PGEs, a subset of individuals with positive SPT to Pt have been shown to have a positive SPT to other PGEs. A survey of 306 South African Pt refinery workers found cross-sensitivity by both SPT and RAST to chlorinated salts of other PGEs in workers that were SPT positive to hexachloroplatinate salts (Murdoch et al., 1986; Murdoch and Pepys, 1987). The authors report that in addition to Pt, refinery workers are known to be exposed to comparable levels of palladium and rhodium salts and that in all cases, refinery workers are exposed other PGEs (Murdoch and Pepys, 1987). Therefore, most Pt refinery studies cannot discriminate between true cross-sensitivity (i.e., individuals with specific IgE antibodies to Pt that also bind and thereby cross-react to other PGEs) and simultaneous development of separate, specific, hypersensitivities to multiple PGEs. No information was reported on symptoms of sensitization or on Pt or other PGE exposure levels at the refinery in Murdoch et al. (1986) or Murdoch and Pepys (1987). SPT were performed to detect sensitivity to hexachloroplatinate and to halogenated salts (not specified) of ruthenium, iridium, rhodium, and palladium. In the 306 total workers, 39 (12.7%) were SPT positive to Pt and a subset of workers that were sensitized to Pt were also sensitized to other PGEs with the following results: two workers (0.6% of 306 total workers) tested positive to palladium; five (1.6% of 306 total) workers tested positive rhodium; 6 (1.9% of 306 total) workers tested positive to iridium; and four (1.3% of 306 total) workers tested positive to ruthenium. Similar results were obtained with compound-specific RAST assays. Cross-reactivity to chlorinated salts of iridium ($IrCl_3$) and rhodium ($RhCl_3$) was also found in some of the 22 workers with positive SPT or patch test to hexachloroplatinic acid among the total population of 153 workers tested in a catalyst manufacturing and recycling factory (Cristaudo et al., 2005). No information was reported on Pt or other PGE exposure levels

at the factory. While 22 of the 153 workers (14.4%) were SPT positive to Pt, only 3 (2.0% of the 153 total) workers were also SPT positive to iridium and 2 (1.31% of the 153 total) of these workers were also SPT positive to rhodium. No worker in the Cristaudo et al. (2005) or Murdoch and Pepys (1987) studies demonstrated sensitization to a PGE that was not also SPT positive to Pt.

As described above, respiratory allergic sensitization as indicated by a positive SPT has been shown for all PGEs except osmium, and it is restricted to individuals who are SPT positive to Pt and in each case occupational exposure to the PGEs takes place in the presence of halogenated Pt salts (Cristaudo et al., 2005; Murdoch and Pepys, 1987; Murdoch et al., 1986). However, there is evidence that other PGEs, especially palladium, are sensitizers independent of co-exposure with Pt compounds. Palladium is a well-known contact sensitizer, particularly from the use of palladium in dental materials (see review in Kielhorn et al., 2002). Evidence of the respiratory sensitizing capacity of palladium is largely limited to occupational studies where co-exposure with Pt cannot be ruled out. There is a single case study of respiratory sensitization to palladium (demonstrated by positive SPTs and specific respiratory challenge to $Pd[NH_3]_4Cl_2$) where it could be demonstrated that exposure was to palladium compounds alone (Daenen et al., 1999). In the case of palladium, there may be a cross-reactivity of antibodies to palladium and nickel, and there is evidence that individuals with nickel allergy are more susceptible to developing allergic sensitization to palladium (Kielhorn et al., 2002).

In summary, several occupational studies demonstrate respiratory sensitization to other PGEs in humans that have a known allergic sensitization to halogenated Pt salts. There is insufficient information to determine if positive SPTs to other PGEs represent cross-sensitization of Pt-specific antibodies rather than separate, specific allergic responses to each PGE or if co-exposure to Pt is important to the development of sensitization to other PGEs. In addition, unlike palladium, there is no evidence that individuals with allergic sensitivity to other metals or PGEs, are more likely to develop sensitization to Pt compounds.

4.6.3.2. *Other Considerations for Mode of Action*

4.6.3.2.1. ***Relevance of particle size to qualitative and quantitative toxicity characteristics of Pt.*** Particle size is an important determinant of deposition, retention, and absorption in the respiratory tract (Oberdörster, 2001, 1994; Oberdörster et al., 2000). Inhalation exposure to Pt has been studied in experimental animals, but no studies examining the relationship between particle size and toxic effects were located. Presumably, smaller particles will be deposited deeper into the respiratory tract, where absorption may be more efficient. Whether Pt particles deposited in the lung undergo transformation to other compounds, including whether or not such particles could function as a hapten and react with native proteins to become capable of producing allergic sensitization, is not known (Oberdörster, 2001).

The effect of particle size has been investigated for respiratory sensitization to diphenyl-methane-4,4'-diisocyanate (MDI) in guinea pigs (Pauluhn et al., 2000). Respiratory sensitization was examined for intradermal injections (3 × 0.3% MDI) or a 15-minute inhalation exposure to 135 mg MDI/m^3 of a small particle aerosol (1.7 μm MMAD) or a large particle aerosol (3.8 μm MMAD). There was a greater response to the large aerosol for sensitization by either the intradermal or inhalation route. The authors hypothesized that the greater sensitization potency of the large aerosol may be related to a greater fraction of deposition of the larger particles within the upper respiratory tract. The relevance of particle size for the sensitization effects of halogenated Pt salts is unknown.

4.6.3.2.2. ***Utility of biomarkers of Pt exposure.*** Overall, the utility of biomonitoring for Pt exposure is limited, as levels of urinary/serum Pt in nonoccupationally exposed populations are generally low and highly variable (for review, see Begerow and Duneman, 2000). Additionally, analysis of Pt in biological samples indicates only the concentration of elemental Pt, and not the specific chemical compounds to which exposure occurred. Other sources of Pt exposure (e.g., dental alloys, Pt-containing drugs, and Pt from prostheses including breast implants) may confound estimates of true environmental exposures (Maharaj, 2004; Merget et al., 2002). In a recent environmental survey of 1,080 German adults, regression analysis revealed that levels of Pt in urine were significantly correlated with the number of teeth with noble metal dental alloy restorations, more frequent coffee consumption, and upper social class status, but not with traffic-related variables (Benemann et al., 2005).

In an occupational study of workers in a catalytic converter production and recycling plant, Petrucci et al. (2005) measured Pt in airborne PM, and blood, urine, and hair of 106 exposed workers, 21 control workers from the plant's administrative offices, and 25 unexposed controls. Health symptoms or Pt allergic sensitization information were not recorded in the study. The report makes no mention of controlling for Pt exposure from dental devices. Environmental air samples were taken in various sites throughout the plant and associated with specific work processes. Sampling times ranged from 13 to 57 hours and airborne particles were collected using pumps equipped with a PM_{10} sampling head to measure particles with a diameter below 10 μm. Personal air sampler devices worn by individual workers for a full week were also used for all sites and most processes for which environmental samples were collected. Analysis of biological and environmental samples was performed by high resolution-ICP-MS and quantitative-ICP-MS with a detection limit of 0.018 ng/m^3 for airborne samples and 1–3 ng/L for biological samples. Concentrations of total and soluble Pt were highly correlated between stationary samplers and personal sampling devices (r^2 = 0.9667). A strong correlation was also observed between Pt concentrations from environmental air samples and Pt concentrations in urine and hair, but not in blood. The authors suggest that urine samples may be

a viable method of biomonitoring occupational Pt exposure, and that blood is not a suitable for monitoring Pt exposure.

A recent study examined levels of various metals, including Pt, and markers of nasal inflammation in nasal lavage fluid (e.g., neutrophil and epithelial cell counts and IL-8 levels) sampled from 67 children (Schins et al., 2004). Children, who were selected from a larger cohort of 283 children (the basis of selection was not provided in the study), were classified into four groups (A, B1, B2, and C) based on area of residence; subjects in group A lived in a small city in a rural region in Germany (representing the control population), and subjects in groups B1, B2, and C lived in two major cities in Germany. "Personal characteristics" for participating subjects were obtained through parent-completed questionnaires. Subjects with hay fever or a specific allergy, diagnosed based on questionnaire and a positive SPT to five common allergens (not reported), were excluded from the study. Nasal lavage was conducted on all participants and analyzed for total cell counts, differential counts (neutrophils, eosinophils, monocytes, lymphocytes, and epithelial cells), IL-8, and concentrations of Pt, vanadium, chromium (measured by sector field ICP-MS; LOD for Pt was 0.01 ng/L). Air monitoring data (daily averages) on traffic-associated air pollutants (airborne PM, NO, NO_2, and CO) were obtained from an air quality monitoring agency, but were not verified in this study. Statistically significant correlations were found between concentrations of Pt (but not concentrations of vanadium or chromium) in the nasal lavage fluid and two cell concentrations associated with inflammation (neutrophil counts [$r = 0.40$, $p < 0.001$] and epithelial cell counts [$r = 0.41$, $p < 0.0001$]). No significant correlations were found between concentrations of any of the metals and IL-8 concentrations in the nasal lavage fluid samples. Air monitoring data indicated that area B1 had significantly higher air pollutant levels (PM, NO, NO_2, and CO) and area C had significantly higher NO_2 and CO levels than area A, but no correlations were found between these indices of air pollution and the concentrations of Pt, vanadium, or chromium in fine or coarse PM samples from the locations. Concentrations of vanadium, chromium, and Pt in nasal lavage fluids were detectable in 64, 73, and 93% of the children, respectively, but significant differences between locations were not found. Although the results show a correlation between Pt concentrations in nasal lavage fluid and neutrophil and epithelial cell counts associated with nasal inflammation, they do not clearly establish whether Pt itself or some other compound or material caused the effect. In addition, the results are limited to the markers of inflammation examined (i.e., differential cell counts from nasal lavage and IL-8) and data were not collected on a more extensive set of cytokines or other inflammatory indicators, nor do they distinguish what form or forms of Pt (e.g., Pt metal, oxides, or soluble halogenated compounds) were present. Although nasal (or pulmonary) inflammation from airborne Pt particles is plausible, the study was unable to conclusively demonstrate inflammation and did not show an association between Pt exposure and Pt concentrations in nasal fluid. Without a more clearly demonstrated association between Pt exposure and effect, or corroborative findings from other studies, the

results provide inadequate evidence to establish nasal inflammation or Pt concentrations from nasal lavage as biomarkers of Pt exposure.

4.6.3.2.3. ***Potential for olfactory nerve uptake.*** Certain metals gain access to the central nervous system via uptake by the olfactory nerve. In rodents following intranasal instillation, certain metals (including manganese, cadmium, nickel, zinc, and mercury) are taken up by the primary olfactory neurons in the olfactory epithelium of the nose and transported along the neurons to the olfactory bulbs in the brain (Persson et al., 2003; Tjälve and Henriksson, 1999; Tjälve et al., 1996). Some metals (e.g., manganese and nickel) appear to be transported via this olfactory pathway to other parts of the brain, whereas other metals (e.g., cadmium and mercury) are not (Tjälve and Henriksson, 1999). Data examining the ability of Pt metal or Pt compounds to be transported via this olfactory pathway to the brain were not located. Furthermore, available data do not provide evidence of neurotoxicity in humans or animals exposed to inhaled soluble or insoluble Pt compounds.

4.6.3.2.4. ***Bioaccumulation of Pt and implications for health effects.*** No data associating the bioaccumulation of Pt to adverse health effects were located. However, two points suggest the need for further consideration. First, studies in rats show that inhaled Pt is preferentially distributed to kidney, liver, spleen, and bone, which suggests the potential for accumulation in these organs (Moore et al., 1975a). Second, a study of occupationally exposed workers showed elevated levels of urinary Pt, 2–6 years following removal from exposure (Schierl et al., 1998). Although these findings suggest that bioaccumulation of Pt is possible, the health effects (if any) of this accumulation are not known.

4.6.3.3. ***Mode of Action Summary***

Exposure of humans and experimental animals to halogenated Pt salts and Pt compounds demonstrates that the immune system is a target organ to halogenated Pt salts. Available data demonstrate that allergic sensitization to Pt compounds is associated with exposure to halogenated Pt salts and do not support sensitization from exposure to insoluble or nonhalogenated Pt compounds. The symptoms and time-course of the allergic sensitization response to halogenated Pt salts are typical of IgE-mediated, Type I allergic response. Data from both humans and animals demonstrate that allergic sensitization results from inhalation exposure. Although data on dermal exposure in humans are lacking, animal data (Kimber and Dearman, 2002; Dearman et al., 1998; Schuppe et al., 1997a) suggest that dermal exposure may also contribute to respiratory allergic sensitization to soluble halogenated Pt compounds.

Research supports a mode of action for low molecular weight compounds, such as soluble halogenated Pt compounds, to act as haptens to produce allergic sensitization (Sarlo and Clark, 1992). Because soluble halogenated Pt compounds are too small to be recognized by the

immune system, they must bind to a larger endogenous substance to form an antigenic complex (Rosner and Merget, 1990). Therefore, the probability that a given Pt compound would be a sensitizer depends on the strength of the Pt ligand bond and its ability to react with endogenous proteins (Linnett and Hughes, 1999; Cleare et al., 1976). The fact that evidence of sensitization is restricted to halogenated Pt salts supports the importance of the reactive halogen groups. Specific proteins involved with the Pt-protein complex have not been identified; however, Linnett and Hughes (1999) hypothesized that, in humans, the most likely site of the Pt chemical-protein bond would be the sulfur in methionine groups on HSA.

When the immune system recognizes the Pt-protein complex, B lymphocytes produce specific antibodies to the Pt compound. These B lymphocytes undergo class switching from the initial IgG isotype to produce IgE antibodies with the same specificity. The IgE antibodies bind to surface receptors of mast cells and basophils and are thereby distributed in mucosal and epithelial tissues where these cell types are normally located. Individuals with these specific IgE antibodies to halogenated Pt salts are then considered to be sensitized and will be positive for specific IgE tests such as the SPT. Subsequent exposure to the same halogenated Pt salts results in binding by the IgE on the cell surface and triggers degranulation and cellular release of histamine, leukotrienes, prostaglandins, and proteases. The extent of release of inflammatory mediators (number of cells involved, affinity of IgE antibodies, etc.) determines the extent of response and contributes to a local or systemic allergic response.

Symptoms of IgE-mediated, Type I allergic responses include asthma, rhinitis, urticaria, conjunctivitis, dermatitis, and anaphylaxis. These symptoms occur only after a symptom-free latency period during which the allergic sensitization is taking place. The epidemiologic data suggest that sensitization can develop over an exposure period of several months to 13 years (Cristaudo et al., 2005; Merget et al., 2000; Linnet and Hughes, 1999).

4.7. EVALUATION OF CARCINOGENICITY

4.7.1. Summary of Overall Weight-of-Evidence

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the cancer descriptor, "data are inadequate for an assessment of human carcinogenic potential," is appropriate for halogenated Pt salts and Pt compounds. Cancer studies in humans and cancer bioassays in animals exposed to soluble or insoluble Pt compounds were not found. As discussed in Section 4.5.2 (*Genotoxicity*), soluble Pt compounds ($PtCl_4$, $Pt[SO_4]_2$, K_2PtCl_4, H_2PtCl_6) produced gene mutations in prokaryotic and eukaryotic test systems, including bacteriophage, bacteria, CHO cells, and mouse lymphoma cells. However, there is no direct evidence to indicate that exposure to halogenated Pt salts or Pt compounds are carcinogenic in animals or humans, with the exception that intraperitoneal exposure of rats or mice to cisplatin produced increased incidences of animals with tumors. Insoluble $PtCl_2$ tested negative for gene

mutations in the *E. coli* SOS chromotest, mouse lymphoma forward mutation test, and human lymphocyte micronuclei test.

Cisplatin has been classified by IARC (1987) in cancer Group 2A, *probably carcinogenic to humans*, based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (increased incidence of tumors in rats (leukemia) and mice (lung adenomas) following multiple intraperitoneal injections). Although no cancer bioassays are available for other Pt antitumor drugs, mutagenicity assays suggest possible carcinogenic activity similar to that of cisplatin (Sanderson et al., 1996).

4.7.2. Synthesis of Human, Animal, and Other Supporting Evidence

Cancer studies in humans and cancer bioassays in animals exposed to soluble or insoluble Pt compounds were not found, with the exception of rat and animal bioassays with cisplatin.

4.7.3. Mode of Action Information

There is inadequate evidence to indicate that exposure to halogenated Pt salts or Pt compounds is carcinogenic in animals or humans, with the exception of the evidence for the carcinogenicity of cisplatin in rats and mice. Thus, possible modes of carcinogenic action of halogenated Pt salts and Pt compounds are not discussed herein.

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

4.8.1. Possible Childhood Susceptibility

No data were located regarding potential increased susceptibility of children in the development of allergic sensitization to halogenated Pt salts. The database for developmental studies of Pt is limited to a single study involving acute gavage dosing of pregnant ICR Swiss mice with $Pt(SO_4)_2$ (D'Agostino et al., 1984; Massaro et al., 1981; see Section 4.3.1). Although comprehensive developmental endpoints were not examined, the results for $Pt(SO_4)_2$ (exposure-related decreased body weights in offspring) indicate that Pt compounds may be toxic to the developing fetus and neonate. Schins et al. (2004), investigating the relationship between Pt concentrations in nasal lavage fluid and markers of nasal inflammation in a group of children, found statistically significant correlations between Pt concentrations in the nasal lavage fluid and neutrophil and epithelial cell counts, although no association was demonstrated between Pt concentrations in nasal fluid and air. However, results of this study do not provide any information regarding the potential for increased susceptibility of children to allergic sensitization to halogenated Pt salts. The epidemiology studies that have examined health outcomes associated with occupational exposures to Pt compounds provide no information on childhood susceptibility.

4.8.2. Possible Gender Differences

No data were located regarding potential gender differences in the development of allergic sensitization to halogenated Pt salts.

4.8.3. Other

Available epidemiological evaluations of Pt allergic sensitization were primarily conducted in populations of adult workers (>90% males) at Pt refineries and Pt catalyst production plants. More susceptible adults are likely to have been selected out of the work force at these facilities (i.e., healthy worker effect). Given the narrow focus of these studies on relatively healthy adult males, the susceptibility of females, children, immune-compromised subjects, or elderly to sensitization to halogenated Pt salts cannot be determined from these studies.

No other data were located examining the relative sensitivities among potentially sensitive populations with regard to development of allergic sensitization to halogenated Pt salts, with the exception that smokers in refineries (Calverley et al., 1995; Baker et al., 1990; Venables et al., 1989), in a combined refinery and catalyst production plant (Linnett and Hughes, 1999), and in a catalyst production plant (Merget et al., 2000) have increased risk for developing sensitization compared with nonsmokers. It is possible that asthmatic individuals may be at special risk to develop sensitivity to halogenated Pt salts. Merget (2000) reported that preexisting asthma or bronchial hyperresponsiveness was not a risk factor for allergic sensitization to halogenated Pt salts in a prospective study of German catalyst production workers, but cautioned that the number of workers with these preexisting conditions were low in this study. Although no data are available on co-exposure to other relevant irritants or adjuvants in the workers in the epidemiology studies, results of the animal study by Biagini et al. (1986) suggest that ozone promotes development of allergic sensitization to Pt (see Section 4.5.1.1.1 for full study details). In monkeys, inhalation of high concentrations of $(NH_4)_2PtCl_6$ (200 μg/m^3, 4 hours/day, 5 days/week for up to 12 weeks) produced minimal evidence of sensitization (e.g., 1/8 monkeys was positive in hexachloroplatinate SPTs). In contrast, 4/8 monkeys exposed to 1 ppm ozone with 200 μg/m^3 hexachloroplatinate had positive SPTs to Na_2PtCl_6, compared with 0/7 monkeys exposed to 1 ppm ozone alone. These results provide support for the hypothesis that airway damage from exposure to irritant materials in combination with exposure to halogenated Pt salts may promote the development of allergic sensitization.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect - with Rationale and Justification

Oral exposure studies of halogenated Pt salts and Pt compounds are not adequate for the determination of an RfD. The human data available on the oral toxicity of halogenated Pt salts and Pt compounds are limited to a single case study report of the toxic effects resulting from of intentional ingestion of a photographic solution containing 600 mg of potassium tetrachloroplatinate (Cl_4K_2Pt) by a 31-year-old man (Woolf and Ebert, 1991). This individual exhibited elevated liver enzymes, acute oliguric renal failure, metabolic acidosis, fever, muscle cramps, gastroenteritis, rhabomyolisis, and elevated serum levels of neutrophils and eosinophils following ingestion of the photographic solution. All signs of toxicity resolved within 6 days of supportive medical care. No additional reports of oral exposure of humans to halogenated Pt salts or Pt compounds were identified.

The kidney may be a target organ for some Pt compounds based on the limited available short-term and subchronic drinking water and dietary exposure studies in animals (Reichlmayr-Lais et al., 1992; Roshchin et al., 1984; Holbrook, 1976; Holbrook et al., 1976, 1975). However, the available animal data involved exposure to several different Pt compounds, employed few dose levels, and there are no comprehensive subchronic or chronic toxicology studies that include even basic endpoints such as histology. In short-term exposure studies, relative kidney weight was increased by 8% in rats exposed to $PtCl_4$ in drinking water (approximately 44 mg Pt/kg-day) for 4 weeks (Holbrook et al., 1975). Decreased renal function, as indicated by increased plasma creatinine concentration, was observed in rats exposed to $PtCl_4$ in the diet (approximately 6 mg Pt/kg-day) for 4 weeks (Reichlmayr-Lais et al., 1992). Although additional data on potential renal effects of oral exposure are not available, rat intraperitoneal LD_{50} values of 40–50 mg/kg for hexachloroplatinic acid were associated with death due to renal failure and necrotizing renal tubular lesions throughout the renal cortex (Ward et al., 1976). The above observations suggestive of nephrotoxicity are consistent with oral toxicokinetic studies in animals demonstrating renal accumulation of soluble [$Pt(SO_4)_2$ and $PtCl_4$] and insoluble [$PtCl_2$ and Pt metal] environmentally relevant Pt compounds (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975). Extensive clinical experience with parenteral exposure to cisplatin and other Pt-containing anticancer drugs also identified the kidney as a target organ for accumulation and toxicity of these compounds after parenteral exposure (Hartmann and Lipp, 2003).

Possible hepatotoxicity associated with oral exposure to Pt compounds is suggested by changes in activities of two hepatic microsomal enzymes (aniline hydroxylase and aminopyrine demethylase) observed in rats exposed to $PtCl_4$ or $Pt(SO_4)_2$ in drinking water or food (Holbrook et al., 1976, 1975); however, the observed changes were not consistent in direction (i.e., increase

or decrease in enzyme activity) or repeatable across oral exposure studies. Reichlmayr-Lais et al. (1992) also reported a trend for decreased erythrocyte number and hematocrit in rats exposed to $PtCl_4$ in the diet for 4 weeks. No studies on the effects of chronic oral exposure of animals to halogenated Pt salts or Pt compounds were identified.

A series of short-term exposure studies conducted by Holbrook and coworkers (Holbrook et al., 1976, 1975; Holbrook, 1976) evaluated the effects of repeated exposure of male Sprague-Dawley rats to three Pt compounds ($PtCl_4$, $Pt[SO_4]_2$, and PtO_2) for durations of approximately 1 or 4 weeks in drinking water or 4 weeks via the diet. Data show small increases in kidney weight in rats exposed to $PtCl_4$ and $Pt(SO_4)_2$ in drinking water; however, only rats exposed to 1.63 mM $PtCl_4$ in drinking water (≈44.1 mg Pt/kg-day) for 4 weeks demonstrated a statistically significant increase in kidney weight (i.e., 8% increase in relative kidney weight, $p < 0.05$). The authors suggested that dietary administration of ($PtCl_4$, $Pt[SO_4]_2$, and PtO_2) for 1 week may have decreased activity of hepatic microsomal enzymes (aniline hydroxylase and aminopyrine demethylase), while exposure for 4 weeks or longer had no effect or increased activity (Holbrook et al., 1976). However, the inconsistent effects (i.e., increase, decrease, and no change) reported in these studies on activities of the hepatic microsomal enzymes (see Table 4-8) are difficult to interpret and do not reflect a clear effect on the liver. The observation that intraperitoneal dosing with $PtCl_4$ prolonged hexobarbital sleeping time in rats provides further evidence that $PtCl_4$ may alter in vivo cytochrome P450 activity (Holbrook et al., 1976). Limitations in study design (e.g., few doses tested, lack of comprehensive evaluation of endpoints such as histopathology, or the absence of evaluation of standard biochemical or hematological parameters) do not allow for identification of other potential target organs, characterization of dose-response relationships, or comparisons of the relative potency of more-soluble (e.g., $PtCl_4$, $Pt[SO_4]_2$) versus less-soluble Pt compounds (e.g., PtO_2).

Reichlmayr-Lais et al. (1992) exposed Sprague-Dawley rats for 4 weeks to $PtCl_2$ or $PtCl_4$ in diet at estimated daily doses of 0.001–6 mg Pt/kg-day. A trend ($p < 0.06$) was observed in rats treated with $PtCl_4$ for decreased erythrocyte number and hematocrit with approximately 13% decreases observed in the highest dose $PtCl_4$ for both measures. Plasma creatinine was significantly ($p < 0.05$) increased by approximately threefold in the 6 mg Pt/kg-day $PtCl_4$ group, indicating altered renal function. No other measure of renal function or additional information on potential histopathological changes to the kidney or other organs was reported. Decreased erythrocyte count and increased creatinine clearance indicated that 4-week dietary exposure to $PtCl_4$, but not $PtCl_2$, may adversely affect the hematopoietic system and the kidney at the doses tested.

Roshchin et al. (1984) evaluated the effects of a 6-month dietary exposure of rats to Pt and palladium powders at doses of 50 mg/kg-day, as well as a 6-month dietary exposure of rats to $(NH_4)_2PtCl_6$ and a related palladium compound ($Pd[NH_3]_4Cl_2$) at doses ranging from 0.05 to 5 mg/kg-day. Treatment effects included reduced body weight gain, decreased prothrombin

time, increased and decreased serum levels of urea, and decreased β-lipoproteins, although specific data on dose-response were not reported. Histopathological examinations of tissues were not conducted. No additional details were reported (e.g., rat strain, sex, number of animals, preparation of dosing material, magnitude of effect). Because the methods and results of the Roshchin et al. (1984) study were not completely reported, it is unclear if the treatment-related effects observed were from Pt or palladium compounds. In addition, it is unclear if effects were specific for oral exposure or inhalation exposure, which was also evaluated in this study.

In summary, available animal studies identify the kidney as a potential target organ for the toxicity of soluble and insoluble Pt compounds, although the available information is insufficient to fully characterize toxicity outcomes or dose-response relationships. Roshchin et al. (1984) observed epithelial swelling in renal convoluted tubules in rats following acute oral administration of 25 mg/kg fine powder of Pt group metals (Pt and/or palladium; 1–5 μm diameter). Although additional data on potential renal effects of acute oral exposure are not available, rat intraperitoneal LD_{50} values of 40–50 mg/kg for hexachloroplatinic acid were associated with death due to renal failure and necrotizing renal tubular lesions throughout the renal cortex (Ward et al., 1976). In short-term exposure studies, relative kidney weight was statistically significantly increased by 8% in rats exposed to 1.63 mM $PtCl_4$ in drinking water for 29 days (approximately 44.1 mg Pt/kg-day) (Holbrook et al., 1975). Decreased renal function, as indicated by increased plasma creatinine concentration, was observed in rats exposed to 50 mg Pt per kg diet as $PtCl_4$ (equivalent to approximately 6 mg Pt/kg-day) for 4 weeks (Reichlmayr-Lais et al., 1992). These observations are consistent with toxicokinetic studies demonstrating that both soluble and insoluble environmentally relevant Pt compounds accumulate in the kidney following oral exposure to soluble [$Pt(SO_4)_2$ and $PtCl_4$] or insoluble [$PtCl_2$ and Pt metal] Pt compounds (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975). Derivation of an RfD based on nephrotoxicity from this relatively limited database of studies would likely result in a cumulative uncertainty factor (UF) of 10,000 or greater (database, subchronic to chronic, LOAEL to NOAEL, animal to human, and human variation). Therefore, an oral RfD was not derived for Pt.

5.2. INHALATION REFERENCE CONCENTRATION (RFC)

5.2.1. Choice of Principal Study and Critical Effect - with Rationale and Justification

Effects in humans resulting from inhalation of Pt include respiratory irritation and effects associated with allergic sensitization. Typical Pt allergic sensitization to halogenated Pt salts includes a range of effects. WHO (2000) lists the following pattern of effects following occupational exposure to halogenated Pt salts: allergic asthma (an inflammatory disorder of the airways that results in shortness of breath), rhinitis (runny nose and sneezing), cough, wheeze, dyspnoea (or difficulty breathing) and cyanosis (bluish skin due to insufficient oxygen in blood)

characteristic of severe asthma, watering of the eyes, itching, urticaria (swollen itching skin), and contact dermatitis (itching skin eruptions) Among the various effects characteristic of Pt-specific allergic sensitization, five main effects (asthma, rhinitis, conjunctivitis, urticaria, and dermatitis) are reported in numerous case reports and occupational studies that identify health effects in workers exposed to halogenated Pt salts (Cristaudo et al., 2005; WHO, 2000, 1991; Merget, 2000; Merget et al., 2000, 1999, 1988; Calverley et al., 1999, 1995; Bolm-Audorff et al., 1992; Baker et al., 1990; Pepys, 1984; Pepys et al., 1972; Marshall, 1952; Hunter et al., 1945). Additional reports provide support for one or more of the above effects (e.g., asthma—Merget et al., 1996, 1995, 1994, 1991; Brooks et al., 1990) or other related effects such as respiratory difficulties (Karasek, 1911), inflammatory changes in the respiratory tract (Merget et al., 1996; Roberts, 1951), bronchospasms (Calverley et al., 1999), and bronchial hyperactivity (Merget et al., 1991; Brooks et al., 1990; Biagini et al., 1985a). Health effects not related to respiratory irritation or allergic sensitization have not been reported in occupational studies involving inhalation exposure to Pt compounds.

Symptoms consistent with allergic sensitization have been observed in workers exposed to Pt in several types of work environments including photographic studios using halogenated Pt salts (Hunter et al., 1945); jobs applying halogenated Pt salts by brush to anodes (Harris, 1975); refinement of Pt involving halogenated Pt salts (Raulf-Heimsoth et al., 2000; Santucci et al., 2000; Linnett and Hughes, 1999; Newman Taylor et al., 1999; Calverley et al., 1999, 1995; Merget et al., 1999, 1996, 1994, 1991, 1988; Niezborala and Garnier, 1996; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990; Venables et al., 1989; Biagini et al., 1985a; Jarabek et al., 1984; Dally et al., 1980; Hughes, 1980; Cromwell et al., 1979; Cleare et al., 1976; Milne, 1970; Parrot et al., 1969; Roberts, 1951; Hunter et al., 1945); and exposure to halogenated Pt salts in the production of Pt catalysts (Cristaudo et al., 2005; Merget et al., 2002, 2001, 2000, 1999, 1996, 1995; Raulf-Heimsoth et al., 2000). Allergic sensitization from occupational exposure via inhalation to halogenated Pt compounds is a well-established human health hazard (WHO, 2000, 1991).

Although the particular Pt compound or compounds involved in many occupational exposures has not been conclusively demonstrated, evidence suggests that allergic sensitization is restricted to halogenated Pt salts (Merget and Rosner, 2001; WHO, 2000, 1991). One factor contributing to the identification of chloroplatinates as relevant compounds in Pt-specific allergic sensitization is knowledge of the chemistry involved in the production of Pt compounds in refineries and catalyst production plants. For example, inhalation exposure to Pt compounds in a Pt refinery includes exposure to halogenated Pt salts (either the complex halogenated Pt salt ammonium hexachloroplatinate, $(NH_4)_2PtCl_6$, or sodium hexachloroplatinate, $NaPtCl_6$) because Pt is precipitated in the form of a complex halogenated Pt salt in whatever method is used in refining (Parrot et al., 1969; Hunter et al., 1945).

Another factor in the identification of Pt compounds responsible for Pt-specific allergic sensitization is the test used to identify Pt-specific allergy. The SPT used to identify individuals with allergic sensitization involves applying a small amount of the challenge substance to the skin, and then the skin is pricked to introduce the substance into the epidermis (described in detail in Section 4.1.2.1.1). Use of the SPT to identify workers with Pt-specific allergic sensitization involves positive response to challenge with chlorinated Pt salts. Therefore, the test for sensitization to Pt compounds is, by definition, a determination of sensitization to chlorinated Pt salts, rather than to soluble Pt compounds in general.

Additional SPT data suggest that Pt-specific allergic sensitization is associated with halogenated Pt salts, rather than chlorinated Pt salts. In a study of workers with Pt-specific allergic sensitization, Cleare et al. (1976) demonstrated that the SPT was positive to halogenated Pt salts including Pt salts with either chlorine or bromine ligands. These results also provide some evidence that halogenated Pt salts may have different sensitizing potencies. Cleare et al. (1976) reported increasing response associated with an increasing number of chlorine atoms (i.e., a stronger response to hexachloroplatinic acid [H_2PtCl_6] than to Pt tetrachloride [$PtCl_4$]) among chlorinated Pt compounds. The results from Cristaudo et al. (2005) also support the increasing allergenicity of Pt compounds associated with increasing number of chlorine atoms, where 22 of 153 workers were SPT positive to H_2PtCl_6 and a subset of these 22 individuals had positive SPTs to Na_2PtCl_6 (11/22) and K_2PtCl_4 (12/22).

In vitro and experimental animal data also provide evidence that Pt-specific allergic sensitization is associated with exposure to halogenated Pt salts. Proliferation and cytokine release in response to halogenated Pt salts were demonstrated an in vitro study reporting immune responses associated with allergic sensitization in isolated human PBMCs (Di Gioacchino et al., 2004). Supportive evidence for the allergenic activity of halogenated Pt salts is also provided by evidence for allergic sensitization and airway effects of inhaled hexachloroplatinate in monkeys (Biagini et al., 1986, 1985b, 1983). Dermal and parenteral studies conducted in animals provide further support of the allergenicity of halogenated Pt salts (Dearman et al., 1998; Schuppe et al., 1997a, b, 1992).

The restriction of Pt-specific allergic sensitization to halogenated Pt salts, rather than just soluble Pt is supported by data from Cleare et al. (1976) demonstrating that non-halogenated soluble Pt compounds such as $K_2Pt(NO_2)_4$ were negative in the SPT in individuals positive to halogenated Pt salts. No studies were located that demonstrate a positive SPT to a non-halogenated Pt compound.

As reviewed earlier in Section 4.1, insoluble forms of Pt (Pt metal and PtO_2) are generally considered to be inert and not anticipated to be associated with allergic sensitization (ACGIH, 2001; Gebel, 2000; WHO, 2000, 1991). In contrast to the numerous studies evaluating health effects associated with exposure to soluble Pt compounds, only one report evaluating the health effects of human exposure to inhaled insoluble Pt compounds was identified (Hunter et

al., 1945). Findings of this study suggest that insoluble Pt compounds do not induce allergic sensitization. Limited evidence also supports the lack of allergenic potential of insoluble Pt compounds. Hunter et al. (1945) reported that occupational asthma was not observed in workers primarily exposed through processes that involved exposure to airborne, insoluble Pt metal. Furthermore, results of the in vitro study by Di Gioacchino et al. (2004) indicate that insoluble $PtCl_2$ did not have immune effects associated with allergic sensitization (proliferation or cytokine release from isolated human PBMCs), whereas halogenated Pt salts demonstrated immune activity in this model.

Data suggest that sensitization to the halogenated Pt salts may be related to the halogen-ligands coordinated to Pt and the negative charge of these complexes (Nischwitz et al., 2004; Ravindra et al., 2004; Rosner and Merget, 2000; Cleare et al., 1976). The reactivity of these Pt coordinated halogen-ligands with proteins is important in the generation of Pt-specific immune response because low molecular weight chemicals such as Pt must act as haptens by binding with larger endogenous substances before they can generate an allergic response (see Sections 4.6.3.1.1–4.6.3.1.3 for a detailed description of haptens and the Type I allergic response). Support for the importance of this reactivity of Pt coordinated halogen-ligands is provided by evidence suggesting that tetraamine Pt dichloride may not cause Pt-specific allergic sensitization. Results of the retrospective occupational exposure study by Linnett and Hughes (1999) show that exposure to tetraamine Pt dichloride alone was not associated with sensitization in workers, whereas mixed exposure to tetraamine Pt dichloride and halogenated Pt salts (chloroplatinates) was associated with allergic sensitization. Similar results were reported by Steinfort et al. (2008) in a prospective study of workers at a catalyst manufacture plant in Melbourne, Australia, where no cases of positive SPT were reported among workers with reported exposure to $[Pt(NH_3)_4]Cl_2$. It is important to note that the Linnett and Hughes (1999) and Steinfort et al. (2008) studies do not include exposure data on the particular Pt compounds to which workers were exposed, and workers were instead classified by work area without speciated Pt exposure data. Halide is present as an ion in tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) and not a ligand coordinated to Pt; therefore, $[Pt(NH_3)_4]Cl_2$ is a halogenated complex, not a halogenated Pt salt (Linnett and Hughes, 1999; Cleare et al., 1976). The Pt in $[Pt(NH_3)_4]Cl_2$ is bonded to nitrogen and ligand substitution necessary to react with proteins is extremely slow and may not take place on a biologically relevant timescale (Cleare et al., 1976). Parenteral studies in animals also provide evidence supporting the findings of Linnett and Hughes (1999) that tetraamine Pt dichloride may not have sensitization properties (Schuppe et al., 1997b).

In summary, the allergenic activity of Pt is compound-dependent and sensitization effects appear to be restricted to the halogenated Pt salts. There is no evidence of allergic sensitization following exposure to insoluble Pt compounds. Although exposure data in occupational studies are only characterized to the extent that soluble Pt concentrations are reported, the specificity of

the SPT used to identify Pt-specific allergic response demonstrates that occupational allergic sensitization from exposure to Pt compounds is to chlorinated Pt salts. Furthermore, the wider application of Pt-specific allergic sensitization to halogenated Pt salts rather than chlorinated Pt salts is suggested by the data from Cleare et al. (1976) and Cristaudo et al. (2005) demonstrating that workers with Pt-specific allergic sensitization may have a positive SPT to chlorinated or brominated Pt salts.

Most of the case reports and occupational studies that detail Pt allergic sensitization do not contain exposure data. Five epidemiologic studies do provide some exposure information on total and soluble Pt along with relative incidence of allergic sensitization to halogenated Pt salts in Pt refinery workers (Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990) and Pt catalyst production workers (Merget et al., 2000; Linnett and Hughes, 1999). These studies are discussed below.

Bolm-Audorff et al. (1992) described a cross-sectional study of the employees of a Pt refinery in Germany in which a cohort of 65 workers was divided into three exposure categories (high, moderate, and low) on the basis of predicted Pt exposure level. Exposure categories were defined based on the job location of workers, rather than personal air monitoring data. The incidence of work-related symptoms (conjunctivitis, rhinitis, coughing, or respiratory distress) was elevated in the high-exposure group (11/21) relative to the moderate- (1/23) and low-exposure (3/21) groups; however, a NOAEL for allergic sensitization to halogenated Pt salts was not identified. Individuals with work-related symptoms of respiratory allergy had a higher incidence of positive SPT with K_2PtCl_6 than workers in the other exposure groups (64.3, 20.0, and 2.5% respectively) as well as higher total IgE and Pt-specific IgE levels. This study reported the occurrence of cases of sensitization to halogenated Pt salts in a workplace in which air concentrations of soluble Pt appeared to have been below the German occupational exposure limit of 2 μg soluble Pt/m^3 (8-hour TWA). However, the exposure data are too limited to reliably estimate the air concentrations experienced by workers in the three exposure categories and the personal air monitoring was only done for a 1-hour period with two filter press workers. Thus, no exposure-response relationship for development of Pt allergic sensitization can be derived from this study.

Linnett and Hughes (1999) studied the incidence of allergic sensitization associated with exposure to two types of soluble Pt compounds, halogenated Pt salts (principally chloroplatinates) and tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$), in a retrospective study of medical surveillance data collected over a 20-year period at a Pt processing facility in the United Kingdom. Exposure categories were defined based on different operations at the same site involving: (1) chloroplatinates in the refinery area, (2) tetraamine Pt dichloride in the autocatalyst production area, or (3) a mixed exposure to chloroplatinates and tetraamine Pt dichloride in the tetraamine Pt dichloride production laboratory. No data on Pt speciation were provided to substantiate that Pt exposure in the refinery area was restricted to chloroplatinates,

that there was mixed exposure in the laboratory, or that exposure in the autocatalyst production area was restricted to tetraamine Pt dichloride. The characterization of Pt sensitization included specific respiratory challenge and diagnosis of Pt-related symptoms at work by a physician as Pt-specific SPT to halogenated Pt salts ($[NH_4]_2PtCl_6$, Na_2PtCl_6, and Na_2PtCl_4) and tetraamine Pt dichloride. The results show that the cumulative probability of allergic sensitization was over 50% after 5 years of exposure in the refinery area where only 2.4% of over 8,000 air samples were above 2 µg soluble Pt/m^3 and Pt exposure was primarily to chloroplatinates. Similarly, the cumulative probability of allergic sensitization was 33% after 5 years of exposure in the refinery area where 28.5% of over 511 samples were above 2 µg soluble Pt/m^3 and exposure was to both chloroplatinates and tetraamine Pt dichloride. In the autocatalyst production area, where air concentrations of soluble Pt were intermediate and tetraamine Pt dichloride was the primary compound, the authors calculated a zero probability of allergic sensitization. Thus, tetraamine Pt dichloride does not show any strong evidence of being a sensitizer. No exposure-response relationship for development of Pt allergic sensitization to halogenated Pt salts can be derived from this study and the study does not identify a NOAEL.

Baker et al. (1990) and Brooks et al. (1990) reported results from a single cross-sectional health study evaluating workers for allergic sensitization to halogenated Pt salts in workers in a U.S. precious metals reclamation plant in 1981 (Baker et al., 1990; Brooks et al., 1990). Pt salt concentrations were reported (as an 8-hour TWA) for air samples collected by the company in a number of work areas during several workdays between 1977 and 1979; the number of sampling days varied with sampling location and ranged from 1 to 9 days. The air samples were collected by stationary air sampling techniques; personal air samples for workers in this study were not collected. The study report did not specify the analytical methods used to determine the Pt salt concentrations in the collected air samples or report the limit of detection. Among current workers, positive SPT results were reported in all areas of the facility, except the offices and the incidence of allergic sensitization to halogenated Pt salts was correlated with the mean air concentrations of the individuals work areas (Spearman correlation = 0.71; $p = 0.11$). Work area concentrations of Pt salts were higher (0.6 µg Pt/m^3 Pt salts) for the group of 15 office workers who were not sensitized than for groups of workers who were sensitized (e.g., 0.4 µg Pt/m^3 for the analytical laboratories). Thus, a reliable NOAEL for allergic sensitization to halogenated Pt salts was not identified in this study, and the cross-sectional design does not allow assessment of the subsequent health status of these workers or the status of office workers who may have left the workplace before the survey. Additionally, no information was provided as to the exclusion of atopic individuals or those with positive SPTs prior to employment in the designated work areas.

The study by Merget et al. (2000) tested baseline allergenic sensitivity to halogenated Pt salts among 275 new and current workers with reassessment after 5 years of follow-up. Conversion to a positive SPT to the halogenated Pt salt hexachloroplatinic acid result over the

5-year period was used as an indicator of allergenic sensitization to halogenated Pt salts. For the exposure assessment, workers were assigned to different exposure categories (high, persistent low, intermittent low, no exposure) based on job title and location within the plant. Air monitoring samples were available to quantify Pt exposure to soluble Pt for each category and limited personal monitoring samples were available for the high-exposure group. The study analyses excluded atopic individuals and workers with a positive SPT at the start of the study. Of the 115 workers in the high-exposure category, 13 (11.3%) developed a positive SPT response at the end of the 5-year follow-up period. Median concentrations (with lower- and upper-quartile values noted in parentheses) for the stationary air samples from the high-exposure catalyst production areas were 0.014 (0.008, 0.041) μg soluble Pt/m^3 in 1992 and 0.037 (0.012, 0.064) μg soluble Pt/m^3 in 1993. Personal air monitoring data was limited to 1993 and only collected from the high-exposure group. The median value (with lower- and upper-quartile values noted in parentheses) for personal air monitoring data was 0.177 (0.093, 0.349) μg soluble Pt/m^3, suggesting that stationary air sampling may have underestimated exposure in work areas. Other than one misclassified case in the persistent low-exposure category, no positive SPT responses were reported in the other exposure categories. For the low-exposure areas (subjects in the persistent-low and intermittent-low groups), median (and lower- and upper-quartile) concentrations were 0.0066 (0.0042, 0.0075) μg soluble Pt/m^3 in 1992 and 0.0004 (0.0003, 0.0013) μg soluble Pt/m^3 in 1993.

The allergenic activity of halogenated Pt salts is supported by three inhalation exposure studies in primates and a larger number of dermal and parenteral exposure studies in experimental animals. The results of the three available subchronic animal studies of inhalation exposure to Pt (Biagini et al., 1986, 1985b, 1983) support the possibility that co-exposure to ozone may promote the development of allergic sensitization to halogenated Pt salts. As reviewed in Section 4.5.1 (*Sensitization Studies*), Biagini et al. (1986) reported sensitization in 1/8 monkeys following subchronic exposure to inhaled ammonium hexachloroplatinate alone and in 4/8 monkeys exposed to ammonium hexachloroplatinate plus ozone, compared to 0/7 in those receiving ozone alone. A low response rate is consistent with the characteristics of a Type I allergic response in humans, in which only a fraction of exposed individuals are expected to become sensitized (see Section 4.6.3.1, *Mode of Action Information, Sensitization*). Dermal application of sodium hexachloroplatinate to mice induced dermal hypersensitivity and a lymphocyte secretion profile of cytokines consistent with an allergic response (Dearman et al., 1998; Schuppe et al., 1997a) and parenteral exposure of rats and mice to various chloroplatinates (e.g., Na_2PtCl_6, $[NH_4]_2PtCl_6$, $[NH_4]_2PtCl_4$, K_2PtCl_4,) induced sensitization (Schuppe et al., 1997b, 1992; Murdoch and Pepys, 1986, 1985, 1984a, b). Results of the Schuppe et al. (1997b) study in mice and the Pepys et al. (1985, 1984b) studies in rats showing that tetraamine Pt dichloride ($[Pt(NH_3)_4]Cl_2$) did not exhibit immunogenic activity are consistent with results of the epidemiology study by Linnett and Hughes (1999) showing that no cases of sensitization were

observed among 39 workers exposed to $[Pt(NH_3)_4]Cl_2$ in the production of automotive catalysts. Although available data from animal studies are inadequate to characterize the exposure level-response relationship for induction of allergic sensitization to halogenated Pt salts in animals exposed by inhalation, these studies do demonstrate the potential allergic sensitization by halogenated Pt salts in experimental animals, and thus support the numerous reports of allergic sensitization to halogenated Pt salts in groups of occupationally exposed workers.

Smoking was identified as a risk factor in the development of Pt-specific allergic sensitization in several occupational studies of workers in Pt refineries and catalyst production plants (Cristaudo et al., 2005; Merget et al., 2000; Linnett and Hughes, 1999; Calverley et al., 1995; Baker et al., 1990; Venables et al., 1989). However, it is clear that nonsmokers develop allergic sensitization to halogenated Pt salts in the same occupational environments as do smokers (i.e., Pt refineries as in Linnett and Hughes, 1999; Baker et al., 1990; Brooks et al., 1990; Venables et al., 1989; and catalyst production plants as in Cristaudo et al., 2005; Merget et al., 2000). The adjusted prevalence odds ratio for developing allergic sensitization to halogenated Pt salts for smokers relative to nonsmokers ranges from 1.1 to 4.66 (OR 1.1, 95% CI 0.4–3.0 for workers in a catalyst production plant reported by Cristaudo et al., 2005; OR 4.66, 95% CI 1.55–14.0 for workers in a Pt refinery reported by Venables et al., 1989). The major effect of smoking as a risk factor appears to be that it decreases the time to developing allergic sensitization. Venable et al. (1989) reported that after 3 years of occupational exposure, there was approximately 75% probability that nonsmokers would develop symptoms of allergic sensitization to halogenated Pt salts, whereas it only took 1 year of exposure for smokers to reach the same probability of developing symptoms of allergic sensitization to halogenated Pt salts. Linnett and Hughes (1999) reported similar relative decrease in the time to sensitization for smokers such that nonsmokers had a cumulative probability of developing allergic sensitization to halogenated Pt salts of approximately 20% after 2 years and smokers reached the same 20% probability in <1 year. Merget et al. (2000) reported that 13/115 workers in the high-exposure group developed allergic sensitization to halogenated Pt salts (as determined by positive SPT) during 5 years of the prospective study and no workers in the low-exposure category (0/111) developed allergic sensitization to halogenated Pt salts. At least 1 of the 13 workers that developed allergic sensitization to halogenated Pt salts developed a positive SPT in each of the 5 years of the study (Merget et al., 2000). The Merget et al. (2000) study identified smoking as a risk factor for developing Pt-specific allergic sensitization with an age-adjusted relative risk of 3.9 for individuals in the high-exposure category (95% CI 1.6–9.7). Merget et al. (2000) did not adjust the report of SPT positive individuals in the high-exposure group for smoking (13/115 workers in the high-exposure group developed Pt-specific allergic sensitization as determined by a positive SPT). An adjustment for smoking as a risk factor may result in a reduced adjusted incidence of workers with Pt-specific allergic sensitization; however, it is unlikely that it would effect the identification of the exposure level of the high dose group as a

LOAEL. Therefore, inclusion of smokers in the Merget et al. (2000) data is also unlikely to affect the identification of the exposure level of the low dose group as the NOAEL.

As described above, several epidemiologic studies have found an increased prevalence of workers with allergic sensitization in halogenated Pt salt-contaminated workplaces with estimated air concentrations <2 μg soluble Pt/m^3 (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). However, only Merget et al. (2000) provided adequate exposure assessment data with sufficient documentation of health effects to establish a dose-response relationship. Therefore, the prospective cohort study among German catalyst production workers (Merget et al., 2000) was used as the principal study for the derivation of the chronic RfC. Pt-specific allergic sensitization, as measured by the development of a positive SPT, was deemed a specific endpoint that resulted from exposure to halogenated Pt salts.

The Merget et al. (2000) study was selected as the principal study for the derivation of the chronic RfC for a number of reasons. First, Merget et al. (2000) state that at the concentration of soluble Pt in the low-exposure group no Pt-specific allergic sensitization was observed in workers in these areas. Therefore, although the authors did not identify a NOAEL, the exposure concentration in the low-exposure areas can be considered a NOAEL. The exposure concentration in the low-exposure group from Merget et al. (2000) represents the only reliable NOAEL among the five studies with some exposure information and relative incidence of allergic sensitization to halogenated Pt salts. Second, Merget et al. (2000) provided the most complete exposure data and the only exposure data that can be linked to allergic sensitization for the development of dose-response assessment among the available studies. Bolm-Audorff et al. (1992) included only six total exposure measurements; each sample was obtained from <4 hours of sampling; and the measurements could not be directly related to the three categories of exposure (high, moderate, and low) used by the researchers. Linnett and Hughes (1999) provided relative frequency of exposure levels above and below 2 μg/m^3 of soluble Pt, but absolute concentrations were not reported. Baker et al. (1990) and Brooks et al. (1990) did not report concentrations of soluble Pt for all work areas associated with positive SPTs and reported a higher concentration (0.6 μg/m^3 soluble Pt) in an area associated with no positive SPTs (0/15 in the offices) than in other work-areas associated with positive SPT (e.g., 2/19 and 0.4 μg/m^3 soluble Pt in the analytical laboratories). Third, Merget et al. (2000) identified the lowest median workplace Pt air concentrations (i.e., 0.014 and 0.037 μg soluble Pt/m^3) associated with a statistically significant increase in the incidence of workers with allergic sensitization to halogenated Pt salts. Fourth, Merget et al. (2000) provided more data on duration of exposure than the other available studies. This is, in part, related to the fact that Merget et al. (2000) was the only study with a prospective experimental design that increased the sensitivity of detecting affected individuals compared with the retrospective and cross-sectional design of the other studies. In addition, Merget et al. (2000) presented information on the time between the initial

and final survey as well as the duration of working at the same occupation for individuals who were employed at the start of the study.

Thus, the prospective cohort study among German catalyst production workers (Merget et al., 2000) was used as the principal study for the derivation of the chronic RfC. Pt-specific allergic sensitization, as measured by the development of a positive SPT, was selected as the critical effect resulting from exposure to halogenated Pt salts. No cases of sensitization developed during the 5-year period in 111 workers (persistent and intermittent low-exposure groups) who worked in areas with reported median air concentrations of 0.0066 μg soluble Pt/m^3 in 1992 and 0.0004 μg soluble Pt/m^3 in 1993. Therefore, exposure in the low-exposure group (persistent and intermittent) represents a NOAEL. In addition, 13/115 workers in the high-exposure group developed allergic sensitization as determined by a positive SPT during the 5 years of the study and therefore, exposure in this group represents a LOAEL. Reported median concentrations in stationary air samples in the high-exposure group were 0.014 and 0.037 μg soluble Pt/m^3 in 1992 and 1993.

5.2.2. Methods of Analysis - Including Models (PBPK, BMD, etc.)

Exposure data from a prospective cohort study among German catalyst production workers (Merget et al., 2000) were considered for benchmark dose (BMD) modeling for the development of Pt-specific allergic sensitization, as measured by the incidence of a positive SPT to hexachloroplatinic acid resulting from exposure to halogenated Pt salts. No individuals in the low- and no-exposure groups had a positive SPT, and therefore, exposure concentrations in the low-exposure group were considered a NOAEL. The available data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. A large degree of uncertainty exists when modeling data sets that do not contain at least two non-zero response levels, because a wide range of curves can be drawn through a single point and a control value (Barnes et al., 1995). Therefore, BMD modeling was performed for comparison purposes only and the NOAEL from the low-exposure group was utilized to derive a point of departure (POD). A detailed discussion of modeling for each exposure metric is presented in Appendix B. The predicted concentrations associated with 10% extra risk (and the lower 95% confidence limits or $BMCL_{10}$) from these models are consistent with the choice of the NOAEL from the low-exposure group to derive a POD.

Airborne Pt concentrations were measured for each of the exposure groups using stationary air sampling in 1992 and 1993. Personal air monitoring was performed in 1993 in the high-exposure group only (see Section 4.1.2.1.2 *Toxicity of soluble forms of Pt: epidemiologic evidence of Pt allergic sensitization* for study details). Personal air monitoring data were not used for modeling because of the small sample size and the fact that data collection was restricted to a single year in the high-dose group only.

The raw exposure data used to generate Figure 1 in Merget et al. (2000) were obtained from the lead author of the study and used to calculate the arithmetic means (pooled and unpooled across years), geometric means (pooled and unpooled across years), medians (pooled and unpooled across years), and mid-medians of Pt air concentrations for the three groups of workers in the high-exposure, low-exposure, and no-excess-exposure categories based on their work locations. A detailed discussion of the derivation of these exposure metrics is presented in Appendix B. The exposure data from stationary air samplers in 1992 and 1993 show a large degree of variation both within years and between years (Table 5-1). The arithmetic mean across both years is thought to be the most appropriate representative value for the general class of exposure measurements presented in Merget et al. (2000). Although the geometric mean is a convenient parameter for describing the central tendencies of lognormal distributions, the arithmetic mean concentration is the most appropriate representative value to estimate an individual's long-term average exposure (Crump, 1998; Mage, 1980). The choice of the arithmetic mean concentration as the appropriate exposure measure derives from the need to estimate an individual's long-term average exposure. Therefore, the arithmetic mean across both years (52.9, 3.37, and 0.048 ng soluble Pt/m^3 for the high-, low-, and no-exposure groups, respectively) was selected as the most appropriate metric for these exposure measurements.

Table 5-1. Concentration of soluble Pt for each exposure group in German catalyst production workers

Exposure group		Arithmetic mean[a] (ng soluble Pt/m^3)			Geometric mean[a] (ng soluble Pt/m^3)			Median[a] (ng soluble Pt/m^3)				Incidence of workers with positive SPT
		1992	1993	Pooled	1992	1993	Pooled	1992	1993	Mid-median	Pooled	
High	Mean or median	61.6	41.4	52.9	20.7	27.7	23.5	13.5[c]	36.5[d]	25.5	18.0	13/115
	SE[b]	34.0	9.62	19.7	1.38	1.34	1.25	NA	NA	NA	NA	
	n	16	12	28	16	12	28	16	12	28	28	
Low	Mean or median	6.06	0.675	3.37	5.78	0.376	1.48	6.55[e]	0.400[f]	3.48	2.45	0/111
	SE[b]	0.664	0.211	0.773	1.13	1.62	1.53	NA	NA	NA	NA	
	N	8	8	16	8	8	16	8	8	16	16	
No	Mean or median	0.047	0.050	0.048	0.044	0.050	0.046	0.045	0.050	0.048	0.050	0/48
	SE[b]	0.007	0.000	0.005	1.150	1.000	1.097	NA	NA	NA	NA	
	n	8	4	12	8	4	12	8	4	12	12	

[a]All of the statistics in this table were calculated directly from the raw data used to generate Figure 1 in Merget et al., 2000 as provided by Dr. Merget.
[b]SEs are provided here, but the quartiles provided in Appendix B were regarded as more appropriate indicators of heterogeneity and variability in the medians and mid-medians. See Appendix B for further discussion.
[c]Calculated value equivalent to 0.014 µg soluble Pt/m^3 reported in Merget et al., 2000.
[d]Calculated value equivalent to 0.037 µg soluble Pt/m^3 reported in Merget et al., 2000.
[e]Calculated value equivalent to 0.0066 µg soluble Pt/m^3 reported in Merget et al., 2000.
[f]Calculated value equivalent to 0.0004 µg soluble Pt/m^3 reported in Merget et al., 2000.

As described above, although allergic sensitization from occupational exposure via inhalation to halogenated Pt salts is a well-established human health hazard (WHO, 2000, 1991), most of the case reports and occupational studies that demonstrate allergic sensitization to Pt compounds do not contain exposure data. Even in the available epidemiologic studies that demonstrate increased prevalences of workers with allergic sensitization to halogenated Pt salts with associated exposure data (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990), the measurements of Pt compounds are limited to determination of soluble Pt/m^3 or total and soluble Pt/m^3 and are not further characterized. Although the particular Pt compound or compounds involved in many occupational exposures has not been conclusively demonstrated, evidence suggests that allergic sensitization is restricted to halogenated Pt salts. In each case, the work environment of a Pt refinery or Pt catalyst production plant where individuals become sensitized to Pt compounds involves exposure to chloroplatinates (e.g., ammonium hexachloroplatinate, potassium hexachloroplatinate, and chloroplatinic acid), but the analytical methods only generically identify soluble Pt compounds. One factor contributing to the identification of chloroplatinates as relevant compounds in Pt-specific allergic sensitization is knowledge of the chemistry involved in the production of Pt compounds in refineries and catalyst production plants. Inhalation exposure to Pt compounds in a Pt refinery includes exposure to the complex halogenated Pt salt ammonium hexachloroplatinate $(NH_4)_2PtCl_6$ or sodium hexachloroplatinate $NaPtCl_6$ because Pt is precipitated in the form of one of these complex halogenated salts in whatever method is used in refining (Parrot et al., 1969; Hunter et al., 1945).

Another factor in the identification of Pt compounds responsible for Pt-specific allergic sensitization is the test used to identify Pt-specific allergy. The SPT used to identify individuals with allergic sensitization involves applying a small amount of the challenge substance to the skin, and then the skin is the pricked to introduce the substance into the epidermis. Detailed information on the use of the SPT in the diagnosis of allergic sensitization is provided in Section 4.1.2.1.1 *Toxicity of soluble forms of Pt: Diagnosis of Pt allergic sensitization* and Section 4.6.3.1.4 *Utility of SPT as an endpoint to identify Pt-specific sensitization*. Use of the SPT to identify workers with Pt-specific allergic sensitization involves positive response to challenge with chlorinated Pt salts (e.g., hexachloroplatinic acid $[H_2PtCl_6]$ in Merget et al., 2000; ammonium hexachloroplatinate $[(NH_4)_2PtCl_6]$, sodium hexachloroplatinate $[Na_2PtCl_6]$, and sodium tetrachloroplatinate $[Na_2PtCl_4]$ in Linnett and Hughes, 1999, potassium hexachloroplatinate $[K_2PtCl_6]$ in Bolm-Audorff et al., 1992; and ammonium hexachloroplatinate $[(NH_4)_2PtCl_6]$ and sodium hexachloroplatinate $[Na_2PtCl_6]$ in Baker et al., 1990). Therefore, the test for sensitization to Pt compounds is, by definition, a determination of sensitization to chlorinated Pt salts, rather than to soluble Pt compounds in general, although the exposure data only identifies soluble Pt compounds. The study by Cleare et al. (1976), comparing the responses to various Pt compounds as determined by the results of the SPT in workers with

known allergic sensitization to Pt, is particularly useful in further refining which Pt compounds are important to Pt-specific allergic sensitization. Cleare et al. (1976) demonstrated that the SPT was positive to halogenated Pt salts with increasing response associated with an increasing number of chlorine atoms (i.e., a stronger response to hexachloroplatinic acid [H_2PtCl_6] than to Pt tetrachloride [$PtCl_4$]) among chlorinated Pt compounds. Exchanging bromine for chlorine in halogenated Pt salts also resulted in positive SPTs, with a similar distribution of potency for brominated Pt salts relative to the number of bromine atoms (Cleare et al., 1976). Data from Cleare et al. (1976) also show that non-halogenated soluble Pt compounds such as $K_2Pt(NO_2)_4$ were negative in the SPT. A recent study by Cristaudo et al. (2005) found a similar result where 22 of 153 workers were SPT positive to H_2PtCl_6 and a subset of these 22 individuals had positive SPTs to Na_2PtCl_6 (11/22), K_2PtCl_4 (12/22), $IrCl_3$ (3/22), and $RhCl_3$ (2/22). Limited evidence also supports the lack of allergenic potential of insoluble Pt compounds. Hunter et al. (1945) reported that occupational asthma was not observed in workers primarily exposed through processes that involved very heavy exposure to airborne, insoluble Pt metal. Furthermore, results of the in vitro study by Di Gioacchino et al. (2004) indicate that insoluble $PtCl_2$ did not have immune effects (proliferation or cytokine release from on isolated human PBMCs), whereas halogenated Pt salts demonstrated immune activity in this model. In summary, although exposure data in occupational studies are only characterized to the extent that soluble Pt concentrations are reported, the specificity of the SPT used to identify Pt-specific allergic response demonstrates that occupational allergic sensitization from exposure to Pt compounds is to chlorinated Pt salts. Furthermore, the data from Cleare et al. (1976) and Cristaudo et al. (2005) demonstrated that Pt-sensitized workers as determined by a positive SPT to one halogenated Pt salt may have a positive response to other halogenated Pt salts including brominated Pt salts. Therefore, the exposure data on soluble Pt/m^3 from Merget et al. (2000) and the positive SPT to the halogenated Pt salt hexachloroplatinic acid is used to derive an RfC for halogenated Pt salts.

Merget et al. (2000) was selected as the principal study (Section 5.2.1) and the development of Pt-specific allergic sensitization as determined by a positive SPT to hexachloroplatinic acid was selected as the critical effect as a measure of allergic sensitization to halogenated Pt salts. The arithmetic mean exposure level of the low-exposure group of 3.37 ng soluble Pt/m^3 from Merget et al. (2000) represented the NOAEL used to derive the POD for the development of an RfC for halogenated Pt salts.

5.2.3. RfC Derivation - Including Application of Uncertainty Factors (UFs)

The incidence of positive SPT to hexachloroplatinic acid was selected as the critical effect as a measure of allergic sensitization from the prospective health survey of workers in a German catalyst production plant (Merget et al., 2000) and exposure data from that study were used to derive the RfC for halogenated Pt salts for the reasons described above. The data from

Merget et al. (2000) were of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) were available and only one of the exposure levels had a non-zero response. Therefore, the BMD modeling was done for comparison purposes only, and the RfC is based on a NOAEL of 3.37 ng soluble Pt/m^3. Because the RfC is a standard applicable to continuous lifetime exposure, EPA guidance (U.S. EPA, 1994b) provides mechanisms for adjusting for differences between 8 hour, 5 days/week occupational exposures and non-occupational 24 hour, 7 days/week predicted exposures using the following equation:

$$NOAEL_{ADJ} = NOAEL\ (mg/m^3) \times (VEho/VEh) \times 5\ days / 7\ days$$

where:

$NOAEL_{ADJ}$ is the dosimetrically adjusted NOAEL;
NOAEL is the TWA occupational exposure level at which no adverse effect was observed;
VEho is the human occupational default minute volume (10 m^3/day); and
VEh is the human ambient default minute volume (20 m^3/day).

Therefore:

NOAEL = 3.37 ng soluble Pt/m^3
= 3.37×10^{-6} mg soluble Pt/m^3

$NOAEL_{ADJ}$ = 3.37×10^{-6} mg soluble Pt/m^3 × (10 m^3/day / 20 m^3/day) × 5 days / 7 days
= 1.20×10^{-6} mg soluble Pt/m^3

A total UF of 1,000 was applied to this POD to derive the RfC: 10 for consideration of interindividual variability (UF_H: human variability), 10 for extrapolation from a subchronic study (UF_S), and 10 for database deficiencies (UF_D). The rationale for the application of the UFs is described below.

A default factor of 10 was used to account for variation in susceptibility among members of the human population (UF_H). The population examined in the Merget et al. (2000) study was workers in a German catalyst production plant. As the working population may be healthier than the general population (i.e., the "healthy worker effect"), this population is not expected to represent the variation in susceptibility among the general population. Insufficient information is available to predict potential variability in susceptibility among the general population to sensitization from inhaled halogenated Pt salts.

A default factor of 10 was used to account for uncertainty in extrapolating from a subchronic to chronic (UF_S) exposure duration since the Merget et al. (2000) study, which was selected as the principal study, is 5-year prospective cohort study. The prevalence of the critical effect (i.e., positive SPT as a measure of allergic sensitization to halogenated Pt salts) increases with increasing exposure duration. However, the information from available epidemiologic

studies is inadequate to specify the duration of exposure necessary to cause allergic sensitization to halogenated Pt salts. The duration of exposure necessary to develop allergic sensitization is likely to depend on exposure dose, frequency of exposure, and biological half-life of the allergen (Scott et al., 2002), as well as interindividual variation. As discussed in Section 4.6.3.1 *Mode of Action Information, Sensitization*, a Type I hypersensitivity response requires more than one exposure to develop a response. Hypersensitivity, in general, may develop after relatively few exposures or after years of exposure (as in the data from Merget et al., 2000). There is evidence of allergic sensitization to Pt developing within an exposure duration range of 1 to 108 months from the retrospective analysis of Pt refinery workers by Linnett and Hughes (1999) and a range of 1 to 5 years in the prospective study by Merget et al. (2000). Ten of the 13 individuals who became sensitized to halogenated Pt salts in the Merget et al. (2000) study were newly employed workers and 3 had already worked at the plant before the initial survey (for 68, 16, and 10 months). One of the 13 workers who developed Pt-specific allergic sensitization (i.e., positive SPT) did so during the first year and another worker developed sensitization the second year. Nine workers developed allergic sensitization in the third year, and the last two became sensitized in years 4 and 5 of the study. An incidence rate of 5.9 per 100 person-years was calculated for newly employed workers, and an incidence rate of 2.1 per 100 person-years was calculated for those who had already worked at the plant before the initial survey. In summary, although allergic sensitization may develop with relatively few exposures, evidence suggests that the likelihood of developing allergic sensitization to halogenated Pt salts increases with increasing exposure duration and a UF was, therefore, used to account for uncertainty in extrapolating from a subchronic to chronic exposure.

A UF_D of 10 was used to account for deficiencies in the Pt database. The database includes multiple case reports as well as several epidemiological studies of allergic sensitization from inhalation exposure to halogenated Pt salts to support the prospective cohort study among German catalyst production workers selected as the key study (Merget et al., 2000). Although inhalation exposure is probably the most common route of exposure for the development of allergic sensitization to compounds in general, data support the development of allergic sensitization and respiratory effects including allergic asthma to some chemicals following dermal exposure alone (Kimber and Dearman, 2002). Available data from occupational studies do not allow the determination of the relevance of dermal exposure in the development of allergic sensitization to halogenated Pt salts. Results from animal studies provide evidence to support the numerous reports of allergic sensitization to halogenated Pt salts in groups of occupationally exposed workers including the development of hypersensitivity following dermal application of hexachloroplatinate to mice (Dearman et al., 1998; Schuppe et al., 1997a). In addition to the relevance of dermal exposure to the development of allergic sensitization to halogenated Pt salts, there are two major sources of uncertainty associated with deficiencies in the database. First, there is a lack of data on the potential for inhalation exposure to Pt

compounds to cause adverse effects other than allergic sensitization. There are no inhalation developmental toxicology studies, and the data on reduced body weights in offspring from the only oral developmental study (acute exposure to $Pt[SO_4]_2$ with limited toxicological endpoints) in the database suggests that Pt compounds may be toxic to the developing fetus and neonate. The inhalation (and oral) toxicity database is also lacking a two-generation reproductive toxicity study. Second, there are animal data showing that inhalation exposure to Pt compounds (including $PtCl_4$, $Pt[SO_4]_2$, PtO_2, and Pt metal) results in preferentially distribution of Pt to kidney, liver, spleen, and bone (Moore et al., 1975a).

The potential for Pt accumulation in the kidney is of particular concern because there is some evidence of potential nephrotoxicity associated with Pt compounds following oral exposure (i.e., increased kidney weight and decreased renal function, as indicated by increased plasma creatinine concentration, in rats exposed to $PtCl_4$, (Holbrook et al., 1975; Reichlmayr-Lais et al., 1992). Interpretation of the animal data suggesting nephrotoxicity is complicated by inadequate study design, limited number of Pt compounds tested, and few dose levels such that data were not sufficient for characterizing a dose-response. However, the above observations suggestive of nephrotoxicity are consistent with oral toxicokinetic studies in animals demonstrating renal accumulation of soluble [$Pt(SO_4)_2$ and $PtCl_4$] and insoluble [$PtCl_2$ and Pt metal] environmentally relevant Pt compounds (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975) and the clinical literature on Pt anticancer agents (particularly the nephrotoxicity associated with cisplatin). The analysis of the scientific information available for Pt compounds as a whole supports the utilization of a database UF of 10.

A UF was not needed for extrapolation from animals-to-humans or from a LOAEL to a NOAEL as human data supporting a NOAEL was used as the POD.

The chronic RfC for halogenated Pt salts was calculated as follows:

$$RfC = NOAEL_{ADJ} \div UF$$
$$= 1.20 \times 10^{-6} \text{ mg soluble Pt/m}^3 \div 1000$$
$$= 1.20 \times 10^{-9} \text{ or } 1 \times 10^{-9} \text{ mg soluble Pt/m}^3 \text{ (rounded to one significant figure)}$$

Note that the RfC applies to halogenated Pt salts as available evidence does not support allergic sensitization to insoluble forms of Pt (e.g., PtO_2 or Pt metal) or non-halogenated soluble Pt compounds. The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown.

5.2.4. Previous RfC Assessment

A previous IRIS assessment was not available for halogenated Pt salts and Pt compounds.

5.3. UNCERTAINTIES IN CHRONIC ORAL REFERENCE DOSE (RfD) AND INHALATION REFERENCE CONCENTRATION (RfC)

Risk assessments need to portray associated uncertainty. The following discussion identifies uncertainties associated with the RfC for halogenated Pt salts. As presented earlier in Sections 5.2.2 and 5.2.3, UFs were applied to the POD in order to derive the RfC. Factors accounting for uncertainties associated with a number of steps in the analyses were adopted to account for a diverse population of varying susceptibilities, extrapolating from a subchronic to chronic exposure duration, and database deficiencies. These extrapolations were carried out with current approaches to inform individual steps given the limited occupational data on halogenated Pt salts and Pt compounds.

A limited range of toxicology data is available for the hazard assessment of halogenated Pt salts and Pt compounds, as described throughout the previous chapters (Chapters 4 and 5). For the oral exposure route, human data are restricted to a single case report of intentional ingestion of a photographic solution containing potassium tetrachloroplatinate (Cl_4K_2Pt). No chronic studies (of either oral or inhalation exposure) in animals exposed to Pt compounds are available and only limited subchronic or short-term animal studies of oral exposure to Pt compounds were identified. The kidney may be a target organ for some Pt compounds based on data suggesting an 8% increase in relative kidney weight in rats exposed to $PtCl_4$ in drinking water (Holbrook et al., 1975), increased plasma creatinine concentration indicating decreased renal function in rats exposed to $PtCl_4$ (Reichlmayr-Lais et al., 1992), and toxicokinetic studies in experimental animals demonstrating renal accumulation of soluble and insoluble Pt compounds. The available studies were not suitable for quantitation of effects for various reasons including the fact that studies are restricted to a limited number of Pt compounds, few doses were employed in the available studies, and there are no comprehensive toxicology studies that include even basic endpoints such as histology. Derivation of an RfD for nephrotoxicity from the available data would likely result in a composite uncertainty factor of 10,000 or greater (database, subchronic to chronic, LOAEL to NOAEL, animal to human, and human variation). The lack of a study or studies with adequate dose-response data to derive an RfD with less uncertainty represents a critical data gap in the oral database given the effects demonstrated.

The inhalation database includes several acute and subchronic exposure studies in cynomolgus monkeys designed to investigate allergic sensitization associated with exposure to Pt compounds, several epidemiologic studies (including a single prospective occupational study from which a NOAEL can be identified for development of allergic sensitization to halogenated Pt salts [Merget et al., 2000]), and numerous case reports of workers who developed Pt sensitization after occupational exposure to Pt compounds. There are few acute or subchronic inhalation toxicity studies of animals exposed to Pt compounds, but limitations in study design or reporting do not allow identification of health hazards other than allergic sensitization. Although

the allergenic activity of halogenated Pt salts is supported by inhalation, dermal, and parenteral exposure studies in experimental animals, the available animal data are inadequate to characterize the exposure level-response relationship for induction of allergic sensitization to halogenated Pt salts. Three animal studies of allergic sensitization to Pt by inhalation exposure were located (two subchronic exposure study in primates by Biagini et al. [1986, 1983] and one acute study by Biagini et al. [1985b] also in primates). These primate studies support the possibility that co-exposure to ozone may promote the development of allergic sensitization to halogenated Pt salts. Critical data gaps have been identified and uncertainties associated with data deficiencies are more fully discussed below.

There are several sources of uncertainty that relate to exposure and the exposure measurements of Pt compounds. The first is the identification of the particular Pt compound or compounds associated with allergic sensitization. Although allergic sensitization from occupational exposure via inhalation to halogenated Pt salts is a well-established human health hazard (WHO, 2000, 1991), most of the case reports and occupational studies that demonstrate allergic sensitization to Pt compounds do not contain exposure data. Even in the available epidemiologic studies that demonstrated an increased prevalence of workers with allergic sensitization to halogenated Pt salts and included exposure data (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990), the measurements of Pt compounds are limited to determination of soluble Pt/m^3 or total and soluble Pt/m^3 without characterization of the particular Pt compounds present. Although exposure data in occupational studies is only characterized to the extent that soluble Pt concentrations are reported, the specificity of the SPT used to identify Pt-specific allergic response demonstrates that occupational allergic sensitization from exposure to Pt compounds is to chlorinated Pt salts. The data from Cleare et al. (1976) demonstrated that among occupationally exposed workers an individual with a positive SPT to one halogenated Pt salt may also have a positive response to other halogenated Pt salts including brominated Pt salts.

The second source of exposure-related uncertainty is derived from evidence suggesting variation in the potency of different halogenated Pt salts to induce Pt-specific allergic sensitization. Results of challenges to various halogenated Pt compounds using the SPT in sensitized Pt refinery workers suggest that the degree of allergic reaction was related to the number of chlorine atoms in a series of chlorinated Pt salts, with the highest activity (i.e., IgE-mediated inflammation) associated with greater number of chlorine atoms (Cleare et al., 1976). Exchanging bromine for chlorine appeared to reduce the allergenicity, with a similar distribution of potency as for the chlorine-containing halogenated Pt salts (Cleare et al., 1976). The results from Cristaudo et al. (2005) also support the increasing allergenicity of halogenated Pt salts associated with increasing number of chlorine atoms, where 22 of 153 workers in a catalyst processing plant were SPT positive to H_2PtCl_6 and a subset of these 22 individuals had positive SPTs to Na_2PtCl_6 (11/22) and K_2PtCl_4 (12/22). Data suggest that sensitization to the

halogenated Pt salts may be related to the strength of the Pt ligand bond of halogen-ligands coordinated to Pt and the ability of these complexes to react with endogenous proteins (see Section 4.6.3.1.1 for a detailed description of haptens and the Type I allergic response) (Nischwitz et al., 2004; Ravindra et al., 2004; Rosner and Merget, 2000; Linnett and Hughes, 1999; Cleare et al., 1976). The potential variation in sensitizing potency among halogenated Pt salts is complicated by the lack of exposure data to specifically identify the halogenated Pt salts associated with the development of allergic sensitization.

The third source of uncertainty in the exposure measurements of Pt compounds is the variation in the exposure measurements from Merget et al. (2000). Exposure data from the stationary air samplers were collected for sampling times that varied between 12 and 17 hours. Thus, the reported air concentrations from the stationary air samples represent 12- to 17-hour TWA concentrations. Although the study author indicated that there were three 8-hours shifts over the 24-hour production in the plant and that there were no differences between work shifts or workplace activity (email from Dr. Rolf Merget, Research Institute for Occupational Medicine, Institutions for Statutory Accident Insurance and Prevention, University Hospital Bergmannsheil, Ruhr University, Bochum, Germany to Andrew A. Rooney, U.S. EPA, dated September 23, 2008), there are no data on potential fluctuations in Pt concentrations throughout the workday. The Pt air concentration data from stationary monitors was highly variable, particularly in the high-exposure dose groups. Exposure estimates for workers in the high-exposure group were highly variable (100- and 1,000-fold variations were reported for stationary air and personal monitoring air samples, respectively). The variation in exposure measurements contribute to the uncertainty associated with exposure levels necessary for the development of Pt-specific allergic sensitization in the workers described in Merget et al. (2000). The variation of Pt air concentration measurements in the low-exposure group was lower (60-fold overall, 2.5-fold in the samples from 1992, and 11.5-fold in the samples from 1993) than the variation in the high-exposure group. This variability is due, in part, to the temporal variability of the concentrations from one day to another as well as the spatial heterogeneity due to the placement of the monitors at different locations within the plant. The number of monitors also depends on the year and the dose group. The variability of Pt concentrations from personal monitors is even larger because it also includes variability introduced by the movement of workers among the several areas of the plant. Epidemiologists often call this statistical variation in exposure "measurement error" or "exposure misclassification error". It may also include analytical error, but this is typically a relatively small component. The typical effect of exposure measurement error on dose-response models is to attenuate or flatten the apparent effect of dose on response (Carroll et al., 1995). In lab animal toxicology studies, the doses are determined with relatively much greater precision than in epidemiologic studies such as Merget et al. (2000). Exposure measurement in Merget et al. (2000) is not much more variable than in some other studies. If it were possible to precisely measure the individual exposures, the typical result would be a steeper

dose-response curve than would be calculated by using a single-number summary of the exposure distribution, whether it is the arithmetic mean, median, geometric mean, mid-median, or any other single statistic to characterize the entire distribution of exposures. There are a number of computational statistical methods for adjusting dose-response for exposure measurement error, but these are not implemented in a NOAEL or in BMD Software (BMDS) if BMD modeling had been utilized to derive the POD. Consequently, there are a number of exposure considerations that contribute to uncertainties in the assessment.

Consideration of the available dose-response data to determine an estimate of inhalation exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime led to the selection of a prospective health survey of workers in a German catalyst production plant (Merget et al., 2000) as the principal study, and the increased incidence of Pt sensitization to halogenated Pt salts as the critical effect for deriving the RfC for halogenated Pt salts. Although several epidemiologic studies have found an increased prevalence of workers with allergic sensitization in halogenated Pt salt-contaminated workplaces with estimated air concentrations <2 μg soluble Pt/m^3 (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990), only the study by Merget et al. (2000) provided adequate exposure assessment data with sufficient health effects data to establish a dose-response relationship.

The derived RfC was quantified using a $NOAEL_{ADJ}$ for the POD. The exposure data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) were available from the Merget et al. (2000) study and only one exposure group had a non-zero response as no individuals in either the low or no-exposure groups had a positive SPT. Therefore, the use of a $NOAEL_{ADJ}$ was used for the POD rather than a POD identified by an effect level concentration (i.e., benchmark concentration [BMC]) because of the large degree of uncertainty in modeling data sets that do not contain at least two non-zero response levels as an unlimited range of curves can be drawn through a single point and a control value (Barnes et al., 1995). A POD based on a LOAEL or NOAEL is, in part, a reflection of the particular exposure concentration observed in an occupational study or the exposure concentration or dose at which an animal study was conducted. It lacks characterization of the dose-response curve and for this reason is less informative than a POD defined by an effect level concentration (i.e., BMC) obtained from BMD modeling of appropriate dose-response data.

Heterogeneity among humans is another uncertainty associated with extrapolating doses from occupational exposure studies to non-occupational exposures of the general population. Uncertainty related to human variation also needs consideration in extrapolating dose from a subset or smaller-sized population (e.g., one sex or a narrow range of life stages typical of occupational epidemiologic studies, to a larger, more diverse population). Human variation may be larger or smaller; however, Pt-specific data on human variation in the development of allergic sensitization to examine the potential magnitude of over- or under-estimation is unavailable.

Consideration of smoking as a risk factor represents an uncertainty associated with extrapolating doses associated with the development of Pt-specific allergic sensitization from occupational exposure studies to non-occupational exposures of the general population. Several occupational studies of workers in Pt refineries and catalyst production plants identify smoking as a risk factor in the development of allergic sensitization to halogenated Pt salts (Merget et al., 2000; Linnett and Hughes, 1999; Calverley et al., 1995; Baker et al., 1990; Venables et al., 1989). However, it is clear that nonsmokers develop allergic sensitization to halogenated Pt salts in the same occupational environments as do smokers (i.e., Pt refineries as in Linnett and Hughes, 1999; Baker et al., 1990; Brooks et al., 1990; Venables et al., 1989; and catalyst production plants as in Cristaudo et al., 2005; Merget et al., 2000). The adjusted prevalence odds ratio for developing allergic sensitization to halogenated Pt salts for smokers relative to nonsmokers ranges from 1.1 to 4.66. The Merget et al. (2000) study identified smoking as a risk factor for developing Pt-specific allergic sensitization with an age-adjusted relative risk of 3.9 for individuals in the high-exposure category (95% CI 1.6–9.7). The major effect of smoking as a risk factor appears to be that it decreases the time to developing allergic sensitization. Venable et al. (1989) reported that after 3 years of occupational exposure, there was approximately 75% probability that nonsmokers would develop symptoms of allergic sensitization to halogenated Pt salts, whereas it only took 1 year of exposure for smokers to reach the same probability of developing symptoms of allergic sensitization to halogenated Pt salts. Merget et al. (2000) reported that 13/115 workers in the high-exposure group developed allergic sensitization to halogenated Pt salts (as determined by positive SPT) during 5 years of the prospective study and no workers in the low-exposure category (0/111) developed allergic sensitization to halogenated Pt salts. At least 1 of the 13 workers who developed allergic sensitization to halogenated Pt salts developed a positive SPT in each of the 5 years of the study (Merget et al., 2000). Merget did not adjust the report of SPT positive individuals in the high-exposure group for smoking (13/115 workers in the high-exposure group developed Pt-specific allergic sensitization as determined by a positive SPT). An adjustment for smoking as a risk factor may result in a reduced adjusted incidence of workers with Pt-specific allergic sensitization; however, it is unlikely that it would effect the identification of the exposure level of the high dose group as a LOAEL. Therefore, inclusion of smokers in the Merget et al. (2000) data is also unlikely to effect the identification of the exposure level of the low dose group as the NOAEL.

Data gaps have been identified with regards to general toxicity studies from either oral or inhalation exposure to halogenated Pt salts or other Pt compounds. Although limited animal studies are available that were designed to examine allergic sensitization associated with halogenated Pt salts, the database lacks oral or inhalation exposure subchronic and chronic basic toxicology studies for halogenated Pt salts or other Pt compounds. The database lacks a multigenerational reproductive toxicity study and neurotoxicity studies. Limited developmental toxicity data are available for oral exposure to $Pt(SO_4)_2$, and no developmental toxicity studies

are available for Pt compounds by the inhalation route of exposure. Although the database of case reports and occupational studies supporting allergic sensitization resulting from inhalation exposure to halogenated Pt salts is adequate, information on the role of dermal exposure in the development of allergic sensitization and respiratory effects including allergic asthma is not available. Inhalation exposure is probably the most common route of exposure for the development of allergic sensitization to compounds in general; however, some data support the development of allergic sensitization and respiratory effects including allergic asthma to some chemicals following dermal exposure alone (Kimber and Dearman, 2002). Available data from occupational studies do not allow the determination of the relevance of dermal exposure in the development of allergic sensitization to halogenated Pt salts. Results from animal studies provide evidence to support the numerous reports of allergic sensitization to halogenated Pt salts in groups of occupationally exposed workers including the development of hypersensitivity following dermal application of hexachloroplatinate to mice (Dearman et al., 1998; Schuppe et al., 1997a). The lack of a sufficient study to derive an RfD represents a critical data gap in the oral database given the potential for nephrotoxicity suggested by the toxicokinetic studies demonstrating renal accumulation of soluble [$Pt(SO_4)_2$ and $PtCl_4$] and insoluble [$PtCl_2$ and Pt metal] environmentally relevant Pt compounds, the clinical literature on Pt anticancer agents (particularly the nephrotoxicity associated with cisplatin), and the evidence for increased kidney weight and increased plasma creatinine concentration in rats exposed to $PtCl_4$.

The use of a positive response in the SPT to hexachloroplatinic acid represents an uncertainty as a measure of allergic sensitization resulting from exposure to halogenated Pt salts. As discussed in Section 4.6.3.1.4 *Utility of the SPT as an endpoint to identify Pt-specific sensitization*, close to 10% (10/110) of workers identified as having allergic sensitization to halogenated Pt salts had a negative SPT in the retrospective study of 406 U.K. refinery workers reported by Linnet and Hughes (1999). Among the 10 SPT-negative cases, 1 was positive in a patch test, 1 was positive in a specific bronchial challenge test, 1 had work-related upper respiratory symptoms, and 7 had bronchospasms at work. The SPT detects IgE-mediated, Type-I allergic responses, and responses may be attenuated in individuals that have had prolonged periods of noncontact with the allergen due to reduced levels of IgE. This should not be the case for workers, who would be exposed weekly. In addition, the positive SPTs to Pt reported in follow-up studies as much as 4 years after individuals who had been terminated from their employment (and presumably their exposure to Pt) due to the development of allergic symptoms (Merget et al., 1999) suggest that a period of reduced exposure to Pt is not responsible for the failure of SPTs to identify all individuals sensitized to halogenated Pt salts. The potential for a second, non-IgE-mediated, mechanism to be responsible for allergic sensitization in some individuals is suggested by the existence of both IgE-mediated and non-IgE-mediated hypersensitivity responses to known sensitizers such as diisocyanate (Kimber and Dearman, 2002; Redlich and Karol, 2002; Kimber et al., 1998). Although specific bronchial challenge

(i.e., measurements of hypersensitivity following direct inhalation of Pt compounds) represents the best measure of allergic sensitization, it is rarely done due to the difficulty in performing the assay and the possibility of anaphylactic reactions, and therefore, the health risk associated with the assay in sensitized individuals.

5.4. CANCER ASSESSMENT

As discussed in Section 4.7, studies addressing the carcinogenic effects of Pt or Pt compounds upon which to base a cancer assessment are unavailable. In accordance with U.S. EPA (2005a) *Guidelines for Carcinogen Risk Assessment*, there is "*inadequate information to assess the carcinogenic potential*" of halogenated Pt salts and Pt compounds. Cancer studies in humans and cancer bioassays in animals exposed to soluble or insoluble Pt compounds were not found. As discussed in Section 4.5.2 (*Genotoxicity*), genotoxicity data were limited; however some soluble Pt compounds ($PtCl_4$, $Pt[SO_4]_2$, K_2PtCl_4, $(NH_4)_2PtCl_6$) produced gene mutations in prokaryotic and eukaryotic test systems, including bacteriophage, bacteria, CHO cells, and mouse lymphoma cells, whereas others such as H_2PtCl_6, K_2PtCl_6, and K_2PtBr_6, have yielded conflicting results from different studies or negative results with no significant mutagenic activity. Insoluble $PtCl_2$ tested negative for gene mutations in the *E. coli* SOS chromotest, mouse lymphoma forward mutation test, and human lymphocyte micronuclei test. There is no direct evidence to indicate that exposure to environmentally relevant Pt or Pt compounds is carcinogenic in animals or humans; however, intraperitoneal exposure of rats or mice to the anti-cancer compound cisplatin produced increased incidences of animals with tumors.

Cisplatin has been classified by the International Agency for Research on Cancer (IARC, 1987) in cancer Group 2A, *probably carcinogenic to humans*, based on inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (increased incidence of tumors in rats (leukemia) and mice (lung adenomas) following multiple intraperitoneal injections). Although no cancer bioassays are available for other Pt antitumor drugs, mutagenicity assays suggest possible carcinogenic activity similar to that of cisplatin (Sanderson et al., 1996).

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

The two major uses of Pt compounds are in jewelry and automotive emission control catalysts (catalytic converters), which represent approximately 30 and 46%, respectively, of the worldwide demand for Pt as of 2005–2006 (Johnson Matthey, 2006a; Renner et al., 2005). The use of Pt as a fuel-borne catalyst in diesel fuel vehicles in recent years presents another potential source of environmental Pt. Evidence suggests that vehicles equipped with catalytic converters represent a significant source of Pt in ambient air, especially in areas heavily populated with automotive vehicles (e.g., Fritsche and Meisel, 2004). Estimates of the fraction of the total Pt emitted from catalytic converters as soluble Pt compounds have ranged from <1 to <10% (Moldovan et al., 2002; Artelt et al., 1999b). As discussed in Chapter 2, analytical challenges have so far precluded the determination of the chemical species of Pt released from catalytic converters or Pt in ambient air samples. Analytical techniques are being developed that may provide speciation information to inform the use of this RfC to source emissions data and ambient samples.

The presence of Pt in dental materials and medical treatments represents a separate category of Pt usage wherein exposure is intentional and the potential toxicity of the form of Pt used may relate to its medical role. Insoluble forms of Pt (Pt metal and PtO_2) are generally considered to be inert, thus leading to the use of alloys containing Pt metal in prostheses, including breast implants (ACGIH, 2001; Gebel, 2000; WHO, 2000, 1991). A comprehensive review of pharmacokinetic and toxicological properties of Pt anticancer drugs is beyond the scope of this document, because they are not expected to represent a significant source of environmental exposure to Pt.

Limited toxicokinetic studies in rodents have examined the absorption, distribution, metabolism, and elimination of Pt compounds. In rats, both soluble and insoluble Pt compounds are poorly absorbed following oral exposure. Reported estimates of oral absorption of $PtCl_4$ and Pt metal (Pt-Al_2O_3 complex) are <1% of the administered dose (Artelt et al., 1999a; Moore et al., 1975b, c). Inhaled soluble and insoluble Pt compounds are cleared from the respiratory tract by mucociliary transport and absorption (Moore et al., 1975a). Soluble $Pt(SO_4)_2$ is cleared from the lung more rapidly than insoluble Pt metal and PtO_2, suggesting more rapid absorption of soluble Pt compounds such as $Pt(SO_4)_2$ following inhalation (Moore et al., 1975a).

Once absorbed into the body, both soluble (e.g., $PtCl_4$) and insoluble (e.g., Pt metal) Pt compounds tend to accumulate primarily in the kidney, liver, spleen, and bone (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975). Pt concentrations in kidney were 5–40 times that of liver following oral or inhalation exposure. Following inhalation exposure to ultrafine

particles (e.g., 13 nm) of Pt metal, the Pt concentration in liver was 30 times that of the kidney (Oberdörster, 2001; Oberdörster et al., 2000), suggesting that the tissue distribution of inhaled ultrafine particles of Pt metal may be different than the observed distribution of large (e.g., 1 μm) particles. Parenteral studies with $PtCl_4$ indicate that Pt accumulates in the fetus (Moore et al., 1975a, b), suggesting that other soluble Pt compounds may be transported across the placenta. As an element, Pt is neither created nor destroyed within the body; however, Pt compounds (e.g., $PtCl_4$) can participate in chemical reactions such as hydrolysis, ligand exchange, and formation of revisible and covalent complexes with amino acids, peptides, and nucleic acids. Pt forms complexes with amino, carboxyl, imidazole (e.g., histidine), and sulfhydryl (e.g., cysteine) groups on amino acids (NAS, 1977). As a result, Pt can form complexes with proteins, nucleic acids, and free amino acids. Absorbed Pt compounds may participate in redox reactions; however, direct evidence for this is limited to data from anticancer therapeutics, while data on environmentally relevant Pt compounds is lacking.

Following oral exposure, fecal excretion of unabsorbed Pt is the dominant excretory pathway for ingested soluble and insoluble Pt compounds (Artelt et al., 1999a) and absorbed Pt is excreted in both feces and urine (Moore et al., 1975b, c). Data on elimination of inhaled Pt compounds in humans is limited to a study of Pt refinery and catalyst production workers (Schierl et al., 1998). This study reported Pt in urine of workers who were exposed predominantly to $(NH_4)_2PtCl_6$ and noted what appeared to be bi-phasic excretion kinetics with fast and slow phase half-times of approximately 50 hours and 24 days, respectively. The study also reported the persistence of urinary Pt excretion 2–6 years following cessation of exposure, suggesting the existence of a more slowly eliminated fraction of body burden that may not be reflected in the above elimination half-time estimates. The observation of faster and slower phases of urinary excretion of Pt in humans is consistent with similar observations of multi-phasic elimination of inhaled Pt metal, PtO_2, $PtCl_4$, or $Pt(SO_4)_2$ in rats (Moore et al., 1975a). Inhaled soluble Pt forms such as $PtCl_4$ are excreted from the body more rapidly than insoluble Pt forms such as PtO_2; however, slower excretion of insoluble forms may, in part, reflect slower clearance from the lung.

Numerous case reports have been published describing workers who developed symptoms consistent with Pt-specific allergic sensitization after occupational exposure to Pt compounds by inhalation (reviewed in WHO, 1991). Health effects in humans include respiratory irritation or symptoms of allergic sensitization such as asthma (shortness of breath), rhinitis (runny nose and sneezing), conjunctivitis (burning and itching eyes), urticaria (rash), and dermatitis (itching skin eruptions) (Cristaudo et al., 2005; Merget, 2000; Merget et al., 1999, 1995; Calverley et al., 1999, 1995; Bolm-Audorff et al., 1992; Baker et al., 1990; Merget et al., 1988; Pepys et al., 1972; Hunter et al., 1945). Symptoms consistent with allergic sensitization have been observed in workers exposed to Pt in several types of work environments including photographic studios using halogenated Pt salts (Hunter et al., 1945); jobs applying halogenated

Pt salts by brush to anodes (Harris, 1975); refinement of Pt involving halogenated Pt salts (Raulf-Heimsoth et al., 2000; Santucci et al., 2000; Linnett and Hughes, 1999; Newman Taylor et al., 1999; Calverley et al., 1999, 1995; Merget et al., 1999, 1996, 1994, 1991, 1988; Niezborala and Garnier, 1996; Bolm-Audorff et al., 1992; Baker et al., 1990; Brooks et al., 1990; Venables et al., 1989; Biagini et al., 1985a; Jarabek et al., 1984; Dally et al., 1980; Hughes, 1980; Cromwell et al., 1979; Cleare et al., 1976; Milne, 1970; Parrot et al., 1969; Roberts, 1951; Hunter et al., 1945); and exposure to halogenated Pt salts in the production of Pt catalysts (Cristaudo et al., 2005; Merget et al., 2002, 2001, 2000, 1999, 1996, 1995; Raulf-Heimsoth et al., 2000). Health effects not related to respiratory irritation or allergic sensitization have not been reported in occupational studies involving inhalation exposure to Pt compounds.

Allergic sensitization from occupational exposure via inhalation to halogenated Pt salts is a well-established human health hazard (WHO, 2000, 1991). Several epidemiologic studies have found increased prevalences of workers with allergic sensitization in halogenated Pt salt-contaminated workplaces with estimated air concentrations <2 μg soluble Pt/m^3 (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). However, only Merget et al. (2000) provided adequate exposure assessment data with sufficient health effects data to establish a dose-response relationship. Although exposure data in available occupational studies are only characterized to the extent that soluble Pt concentrations are reported, the specificity of the SPT used to identify Pt-specific allergic response demonstrates that occupational allergic sensitization from exposure to Pt compounds is to chlorinated Pt salts. Furthermore, the data from Cleare et al. (1976) demonstrated that the SPT among occupationally exposed workers may also result in a positive response to other halogenated Pt salts, such as brominated Pt salts.

The mode of action for allergic sensitization to halogenated Pt salts following inhalation exposure is likely to be primarily an IgE-mediated, Type I allergic reaction based on the symptoms and time-course of the hypersensitivity response. However, the possibility that a second, non-IgE-mediated, mechanism is responsible for some cases of allergic sensitization to halogenated Pt salts is suggested by several lines of evidence including pulmonary effects of Pt compounds in naive monkeys (Biagini et al., 1985b) and the failure of skin prick testing to identify all workers displaying symptoms of allergic sensitization to halogenated Pt salts.

6.2. DOSE RESPONSE

6.2.1. Noncancer/Oral

The database for oral exposure to halogenated Pt salts and Pt compounds in humans is limited to a single case report of the toxic effects of intentional ingestion of a photographic solution containing 600 mg of potassium tetrachloroplatinate (Cl_4K_2Pt) (Woolf and Ebert, 1991), and several short-term drinking water and dietary studies in rats (Reichlmayr-Lais et al., 1992; Roshchin et al., 1984; Holbrook, 1976; Holbrook et al., 1976, 1975). All signs of toxicity

(elevated liver enzymes, acute oliguric renal failure, metabolic acidosis, fever, muscle cramps, gastroenteritis, rhabomyolisis, and elevated serum levels of neutrophils and eosinophils) from the individual in the case report resolved within 6 days of supportive medical care following ingestion of the photographic solution.

Possible hepatotoxicity associated with oral exposure to Pt compounds is suggested by changes in activities of two hepatic microsomal enzymes (aniline hydroxylase and aminopyrine demethylase) observed in rats exposed to $PtCl_4$ or $Pt(SO_4)_2$ in drinking water or food (Holbrook et al., 1976, 1975); however, the observed changes were not consistent in direction (i.e., increase or decrease in enzyme activity) or repeatable across oral exposure studies. No studies on the effects of chronic oral exposure of animals to Pt or Pt compounds were identified.

The limited available short-term and subchronic drinking water and dietary exposure studies in rats suggest that the kidney may be a target organ for some Pt compounds. Oral toxicokinetic studies in rats demonstrate renal accumulation of soluble [$Pt(SO_4)_2$ and $PtCl_4$] and insoluble [$PtCl_2$ and Pt metal] environmentally relevant Pt compounds (Artelt et al., 1999a; Reichlmayr-Lais et al., 1992; Massaro et al., 1981; Lown et al., 1980; Holbrook et al., 1975; Moore et al., 1975a, b; Yoakum et al., 1975). The potential for Pt accumulation in the kidney is of particular concern because there is some evidence of potential nephrotoxicity associated with Pt compounds following oral exposure (i.e., increased kidney weight and decreased renal function, as indicated by increased plasma creatinine concentration, in rats exposed to $PtCl_4$) (Holbrook et al., 1975; Reichlmayr-Lais et al., 1992). However, data are restricted to a limited number of Pt compounds, few doses were examined in the existing studies, and no comprehensive subchronic or chronic toxicology studies have been conducted and therefore, there is a lack of basic toxicological data such as histology. Derivation of an RfD for nephrotoxicity from the available data would likely result in a composite UF of $\geq$ 10,000 (database, subchronic to chronic, LOAEL to NOAEL, animal to human, and human variation). The lack of a study or studies with adequate dose-response data to derive an RfD with less uncertainty represents a critical data gap in the oral database given the potential effects that have been demonstrated.

6.2.2. Noncancer/Inhalation

Allergic sensitization from occupational exposure via inhalation to halogenated Pt salts is a well-established human health hazard (WHO, 2000, 1991). There are numerous case reports and occupational studies of workers who develop allergic sensitization to halogenated Pt salts; however, most studies do not include adequate exposure assessment. Of the available data with exposure estimates, several epidemiologic studies found increased prevalences of workers with allergic sensitization in halogenated Pt salt-contaminated workplaces with estimated air concentrations <2 μg soluble Pt/m^3 (Merget et al., 2000; Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). However, only Merget et al. (2000) provided adequate

exposure data along with sufficient health effects data to establish a dose-response relationship. Although available data from animal studies are inadequate to characterize the exposure level-response relationship for induction of allergic sensitization to halogenated Pt salts in animals exposed to Pt compounds via inhalation, the allergenic activity of halogenated Pt salts in humans is supported by three inhalation exposure studies in primates and a larger number of dermal and parenteral exposure studies in experimental animals.

Consideration of the available dose-response data to determine an estimate of inhalation exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime led to the selection of a prospective cohort study among German catalyst production workers (Merget et al., 2000) as the principal study and the development of Pt-specific allergic sensitization as measured by the incidence of a positive skin prick test (SPT) to hexachloroplatinic acid as the critical effect for deriving an RfC for halogenated Pt salts. The arithmetic mean exposure concentration of workers in the low-exposure group in this study represents a NOAEL of 3.37 ng soluble Pt/m^3.

Because the RfC is a standard applicable to continuous lifetime exposure, a dosimetrically adjusted NOAEL ($NOAEL_{ADJ}$) of 1×10^{-6} mg/m^3 was derived from the occupationally identified NOAEL. The RfC was derived from the $NOAEL_{ADJ}$ as the identified POD. A POD based on a LOAEL or NOAEL is, in part, a reflection of the particular exposure concentrations or doses at which a study was conducted. A POD so derived does not make use of the dose-response relationship, and for this reason, is less informative than a POD defined as an effect level concentration (i.e., BMC) obtained from benchmark dose-response modeling.

The RfC of 1×10^{-9} mg/m^3 was calculated from a $NOAEL_{ADJ}$ of 1×10^{-6} mg/m^3 for development of allergic sensitization to halogenated Pt salts as determined by positive SPT to hexachloroplatinic acid (Merget et al., 2000). Note that the RfC applies to halogenated Pt salts as available evidence does not support allergic sensitization to insoluble forms of Pt (e.g., PtO_2 or Pt metal) or non-halogenated soluble Pt compounds. The use of the RfC for Pt compounds other than halogenated Pt salts is not recommended as the similarity between these compounds and other soluble forms of Pt compounds is unknown. A total UF of 1,000 was used: 10 for intraspecies variability, 10 for subchronic to chronic extrapolation, and 10 for database deficiencies.

Heterogeneity among humans is an uncertainty associated with extrapolating doses from animals to humans. Uncertainty related to human variation needs consideration, also, in extrapolating dose from a subset or smaller sized population, say of one sex or a narrow range of life stages typical of occupational epidemiologic studies, to a larger, more diverse population. Human variation may be larger or smaller; however, Pt-specific data to examine the potential magnitude of over- or under-estimation are unavailable. Therefore, insufficient information is available to predict potential variability in susceptibility among the population; thus, a human variability uncertainty factor of 10 was applied. A 10-fold UF was used to account for

uncertainty in extrapolating from a subchronic to chronic exposure duration. Data gaps have been identified with uncertainties associated with database deficiencies with regards to a lack of general toxicity studies, as well as a lack of reproductive and developmental toxicity studies. Therefore, a database uncertainty factor of 10 was applied, noting the extensive support for Pt-specific allergic sensitization in humans as observed in the principal study, and the similar effects observed in animals, but the general lack of toxicity studies on any other endpoint.

The overall confidence in this RfC assessment is low. Confidence in the principal study (Merget et al., 2000) is low. It is a well-designed, well-conducted, and well-reported prospective epidemiologic study that provided an exposure estimate that represents a NOAEL indicating that no cases of allergic sensitization to halogenated Pt salts developed over a 5-year period in workers in a German catalyst production facility at an exposure concentration of 3.37 ng soluble Pt/m^3. The high variation in exposure measurements (i.e., 100-fold variation in the stationary air samples used for derivation of the RfC and 1,000-fold variation in the personal air samples) and lack of speciation of the soluble Pt measurements reported in Merget et al. (2000) contribute to low confidence in the exposure measurements. BMD modeling of the exposure measurements reported in Merget et al. (2000) was performed for comparison purposes only as the data are of marginal adequacy for BMD modeling because only three exposure groups (high, low, and no exposure) are available and only one of these groups has a non-zero response. Therefore, the NOAEL from the low exposure group in Merget et al. (2000) was utilized to derive a POD for the development of an RfC for halogenated Pt salts. Confidence that Pt-specific allergic sensitization is associated with halogenated Pt salts is high because of the specificity of the SPT for the individual halogenated salts used in Merget et al. (2000) and the other occupational studies with exposure data (Linnett and Hughes, 1999; Bolm-Audorff et al., 1992; Baker et al., 1990). Confidence in the database for allergic sensitization from exposure to halogenated Pt salts is high, whereas confidence in the overall toxicity from exposure to halogenated Pt salts is low. The database of case reports and occupational studies provide strong evidence that allergic sensitization is the critical effect from inhalation exposure to halogenated Pt salts. In addition, animal studies provide further support for allergic sensitization from exposure to halogenated Pt salts. However, several factors limit the overall confidence in the database. The available exposure-response information for the development of allergic sensitization to halogenated Pt salts covers a period of only 5 years, and therefore, a less-than-lifetime exposure duration. In addition, there is a complete lack of information on whether inhalation exposure to halogenated Pt salts or other forms of Pt may induce other systemic, reproductive, developmental, or neurotoxicological effects. In addition, the available occupational data on Pt-specific allergic sensitization are from healthy adult workers (predominately male). The potential susceptibility of young, aged, or asthmatic populations is unknown. The overall confidence in the chronic RfC of low reflects the variation in the exposure data and confidence in the database.

The elicitation dose is generally lower than the dose required to induce sensitization for both contact and respiratory sensitization (see Section 4.6.3.1.7 *Relationship between exposure levels associated with sensitization and the subsequent exposure levels required to elicit a response* for discussion) (Arts et al., 2006). A single dose level of hexachloroplatinic acid (4.1 g/L) was used for elicitation in the SPT; therefore, no information on the dose-response for elicitation is available from Merget et al. (2000). Data from other refinery workers with allergic sensitization to Pt, demonstrate that the elicitation doses required to produce a positive SPT to $(NH_4)_2PtCl_6$ ranged from 10^{-9} to 10^{-3} g/mL (Biagini et al., 1985a). These data suggest that an RfC, derived with standard methods involving application of uncertainty factors to a reliable NOAEL for the induction of halogenated Pt salt sensitization, may not prevent elicitation responses in some previously sensitized individuals. As such, the RfC is expected to be protective against developing allergic sensitization to halogenated Pt salts, but it is not expected to be protective for exacerbation of symptoms in previously sensitized individuals.

6.2.3. Cancer/Oral and Inhalation

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for halogenated Pt salts and Pt compounds is inadequate to assess human carcinogenic potential and to calculate quantitative cancer risk estimates.

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APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

APPENDIX B. BENCHMARK DOSE (BMD) MODELING

B.1. SUMMARY OF BMDS MODELING RESULTS FOR Pt USING THE OUTCOME OF SPTs FROM AN OCCUPATIONAL EXPOSURE STUDY

This appendix summarizes the results of a dose-response assessment carried out using data from a prospective cohort study of German catalyst production workers categorized into three exposure groups (high, low, and no exposure to Pt) and then evaluated for Pt-specific allergic sensitization resulting from exposure to halogenated Pt salts, as measured by a SPT to hexachloroplatinic acid (Merget et al., 2000). All available dichotomous models in U.S. EPA's Benchmark Dose Software (BMDS, version 1.40d) were fit to the data in accordance with U.S. EPA (2000c) BMD methodology.

B.1.1. Exposure Metrics

Airborne Pt concentrations were determined for each of the three exposure groups using stationary air sampling results from 1992 and 1993, and personal air monitoring results from 1993 in the high-exposure group only (see Section 4.1.2.1.2 *Toxicity of soluble forms of Pt: epidemiologic evidence of Pt allergic sensitization* for study details). Personal air monitoring data were not used for BMD modeling because of the limited nature of these data (i.e., personal air monitoring data were collected only in 1993 and in the high-dose group only). All of the BMDS models available were fit employing each of the following exposure metrics from stationary air monitoring data that reported concentrations of soluble Pt (in ng/m^3) in the work areas of the high, low, and no exposure groups in the catalyst production plant:

Arithmetic Mean Pt for 1992
Arithmetic mean Pt for 1993
Arithmetic mean Pt pooled for 1992 and 1993
Geometric mean Pt for 1992
Geometric mean Pt for 1993
Geometric mean Pt pooled for 1992 and 1993
Median Pt for 1992
Median Pt for 1993
Median Pt pooled for 1992 and 1993
Mid-median, unweighted average of 1992 and 1993 medians

The original data as provided by the principal investigator, Dr. Merget, were used to calculate the above statistics as possible exposure metrics for airborne concentrations of soluble Pt. The number of Pt air samples from each worker exposure area during each year is shown in Table B-1:

Table B-1. Number of observations of soluble Pt, as measured by stationary air monitors, for each exposure group by year

Exposure group	Year	
	1992	1993
None	8	4
Low	8	8
High	16	12

In deriving the exposure metrics described above, calculating a pooled median was somewhat problematic. The individual exposure measurements were obtained from Merget, ranked from smallest to largest within each exposure group across years, and then the middle observation in the combined set was selected as the median. The 1992 and 1993 data in the high- and no-exposure groups showed considerable overlap, and pooling the data for both years within each of these exposure groups seemed reasonable. However, the 1992 and 1993 data in the low-exposure group did not overlap, so that pooling data across these 2 years was a matter of concern. Therefore, another exposure metric was constructed, the mid-median, that dealt with this concern. To derive the mid-median, the unweighted average of the medians from 1992 and 1993 was calculated. This is a reasonably robust statistic whose values were consistent with other pooled statistics (median or geometric mean) for both the high-exposure and no-exposure groups. Access to the raw data, instead of the highly aggregated data in the box plots from the figures in Merget et al. (2000), allowed detailed comparison and evaluation of several candidate exposure metrics. The mid-median and the pooled median are probably the more robust estimates with respect to characterizing the distribution of Pt air concentrations than are geometric means.

Exposure metrics were derived from the actual air concentrations of Pt measured at locations within the catalyst production facility described in Merget et al. (2000). BMDS models applicable to quantal (discrete binary) responses that allow use of the logarithm of soluble Pt concentration are the log-logistic and log-probit models. Using the logarithm of concentration was possible because even in the lowest exposure work area, a non-zero Pt concentration existed. Even if an air Pt concentration of 0 had been observed, the functional forms of the log-logistic and log-probit models within BMDS avoid any mathematical problems associated with taking the logarithm of 0. With other dose-response models, using the logarithm of 0 would not be possible. The existence of only non-negative values in the no-exposure group allows all dose metrics to be modeled. The values of the three dose metrics employed are shown in Table B-2.

Table B-2. Three different dose metrics for representing air concentrations of soluble Pt in each of three exposure groups of German catalyst production workers from Merget et al. (2000)

Exposure group		Arithmetic mean[a] (ng soluble Pt/m^3)			Geometric mean[a] (ng soluble Pt/m^3)			Median[a] (ng soluble Pt/m^3)			
		1992	1993	Pooled	1992	1993	Pooled	1992	1993	Mid-median	Pooled
High	Measure of central tendency	61.6	41.4	52.9	20.7	27.7	23.5	13.5	36.5	25.5	18.0
	SE	34.0	9.62	19.7	1.38	1.34	1.25	NA	NA	NA	NA
	LCL or 25th percentile[b]	<0.13	20.2	12.5	10.4	14.4	14.8	7.9	12.0	NA	9.0
	UCL or 75th percentile[b]	134	62.5	93.3	41.5	53.0	37.0	41.5	64.5	NA	52.5
	n	16	12	28	16	12	28	16	12	28	28
Low	Measure of central tendency	6.06	0.675	3.37	5.78	0.376	1.48	6.55	0.400	3.48	2.45
	SE	0.664	0.211	0.773	1.13	1.62	1.53	NA	NA	NA	NA
	LCL or 25th percentile[b]	4.49	0.176	1.722	4.35	0.120	0.594	4.25	0.225	NA	0.40
	UCL or 75th percentile[b]	7.63	1.17	5.02	7.68	1.18	3.67	7.45	1.30	NA	6.55
	n	8	8	16	8	8	16	8	8	16	16
No	Measure of central tendency	0.047	0.050	0.048	0.044	0.050	0.046	0.045	0.050	0.048	0.050
	SE	0.007	0.000	0.005	1.150	1.000	1.097	NA	NA	NA	NA
	LCL or 25th percentile[b]	0.030	0.050	0.038	0.032	0.050	0.038	0.03	0.05	NA	0.035
	UCL or 75th percentile[b]	0.065	0.050	0.059	0.061	0.050	0.056	0.055	0.05	NA	0.05
	n	8	4	12	8	4	12	8	4	12	12

[a]All of the statistics in this table were calculated directly from the raw data used to generate Figure 1 in Merget et al. (2000) as provided by Dr. Merget.
[b]SEs were regarded as not relevant for characterizing the variability of the robust order statistics (medians, mid-medians) used here as air exposure metrics. Quartiles are provided as more appropriate indicators of heterogeneity and variability for the medians and mid-medians, i.e., the 25th percentile instead of a lower confidence limit (LCL) and the 75th percentile in place of an upper confidence limit. See the text for further discussion.

For the no-exposure group in 1992, the median air concentration was 0.045 ng/m^3 soluble Pt, which was not otherwise adjusted for the LOD of 0.05 ng/m^3. For the same exposure group in 1993, the LOD was 0.13 ng/m^3, with all concentrations observed in the no-exposure group

below this limit. Employing the LOD of 0.13 ng/m^3 as a typical value for the non-detects seems less credible than using a smaller value; therefore, the same median concentration of 0.05 ng/m^3 observed in 1992 was employed for 1993, although this made little difference in the analyses.

The Pt air concentration data from stationary monitors exhibits a highly dispersed distribution, particularly in the high-exposure group. This is due, in part, to the temporal variability of the concentrations from one day to the next, as well as to the spatial heterogeneity resulting from the placement of monitors at different locations throughout the plant. The number of monitors employed also varied from year to year and was not consistent across exposure groups. The variability in the distribution of Pt concentrations from personal air monitors is even larger than for stationary monitors because personal monitors include additional variability introduced by movement of workers among several areas of the plant. Epidemiologists often call this variability in exposure "measurement error" or "exposure misclassification error". This variability may also include analytical error, but this is typically small relative to other sources of variability. The typical effect of exposure measurement error on dose-response models is to attenuate or flatten the apparent effect of dose on response (Carroll et al., 1995).

In animal toxicology studies, doses are determined with greater precision than in epidemiologic studies such as Merget et al. (2000). Exposure measurements in Merget et al. (2002) were not much more variable than in other similar studies. If it were possible to precisely measure the individual exposures, the typical result would be a steeper dose-response curve than what was observed, and consequently, a smaller BMC and BMCL for the same benchmark response (BMR) than would have been calculated by using a single summary statistic to represent the entire exposure distribution. A number of computational statistical methods exist for adjusting dose-response for exposure measurement error, but these have not been currently implemented in BMDS. Consequently, uncertainty in the measurement and characterization of exposure is another factor in selecting an appropriate UF for the derivation of the RfC.

B.1.2. Approach for Dose-Response Modeling and Results

The amount of dose-response information contained in these data is very limited. The entire dataset is represented by only three pairs of measurements in the form (x, y), where x is the exposure metric and y is the response (i.e., the incidence of positive SPT). These exposure-response data pairs can be represented as follows: (no-exposure metric, 0), (low-exposure metric, 0), and (high-exposure metric, 13/115). These data suggest the following regarding the dose-response relationship:

(1) the shape of the response at low doses is very flat, essentially a nonlinear function that increases rapidly above the low-exposure metric; thus, one may expect BMDS to estimate 0 as the background response;

(2) the typical BMDS model that can fit these data is sublinear, essentially, below a straight line drawn from (low-exposure metric, 0) to (high-exposure metric, 13/115);

(3) most dose-response functions that increase sufficiently rapidly with increasing dose above the low-exposure concentration will satisfy the BMDS model selection criterion (Akaike's Information Criterion [AIC] within 2 units of the minimum AIC, $p > 0.10$), but model fitting is still useful in eliminating those models that do not fit adequately, and thus do not need to be considered in evaluating uncertainty associated with model selection.

No a priori reason exists to choose data from a single year (i.e., 1992 or 1993), and thus exclude data from the other year. Therefore, only dose metrics representing a combination of the 2 years (i.e., pooled geometric means, mid-medians, pooled medians, and pooled arithmetic means) were considered for use in dose-response modeling. However, exposure metrics representing data from individual years were modeled for comparison purposes.

The BMR was defined as a 10% increase in extra risk because there was no clear biological rationale for selecting an alternate BMR for these data. Employing each of the seven exposure metrics in fitting all available BMDS models yielded very similar BMC and $BMCL_{10}$ values (i.e., all $BMCL_{10}$ values were between 12.9 and 49.4 ng/m^3 soluble Pt). The highest $BMCL_{10}$ value of 49.4 ng/m^3 soluble Pt resulted from the use of the arithmetic mean of pooled data from 1992 and 1993, and was approximately 4 times higher than the lowest $BMCL_{10}$ value of 12.9 ng/m^3 of soluble Pt resulting from the use of the median of pooled data from 1992 and 1993. The BMD modeling results for exposure metrics employing the pooled geometric means, mid-medians, pooled medians, and pooled arithmetic means are presented below in Tables B-3, B-4, B-5, and B-6.

Table B-3. BMD modeling results employing the pooled geometric mean of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric

Model	Power	AIC	*p*	Df *p*	BMC_{10}	$BMCL_{10}$
Weibull	18	83.151	1.0000	2	23.3	16.3
Multistage (Weibull Integer Power)	8	83.151	1.0000	2	23.1	21.9
	7	83.151	1.0000	2	23.1	21.7
	6	83.151	1.0000	2	23.0	21.5
	5	83.151	1.0000	2	22.9	21.0
	4	83.152	0.9999	2	22.7	20.5
	3	83.158	0.9983	2	22.5	19.5
	2	83.257	0.9739	2	22.1	17.8
	1	84.798	0.6530	2	22.0	14.4
Gamma	6.62 ± 128	85.151	0.9986	1	22.7	16.2
Logistic	NA[a]	85.151	0.9996	1	23.3	20.9
Log-Logit	6.16 ± 348.	85.151	0.9994	1	23.0	16.0
Probit	NA	85.151	0.9995	1	23.2	20.2
Log-Probit	1.65 ± 162	85.151	0.9995	1	22.5	14.8

[a]NA means that a model statistic cannot or will not be calculated. The gray shaded models did not attain the model selection criteria used for BMDS.

Df = degrees of freedom

Table B-4. BMD modeling results employing the mid-median of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric

Model	Power	AIC	*p*	Df *p*	BMC_{10}	$BMCL_{10}$
Weibull	18	83.151	1.0000	2	25.3	19.6
Multistage (Weibull Integer Power)	8	83.151	1.0000	2	25.1	23.8
	7	83.151	1.0000	2	25.0	23.6
	6	83.151	1.0000	2	25.0	23.2
	5	83.153	0.9997	2	24.8	22.8
	4	83.160	0.9977	2	24.7	22.2
	3	83.219	0.9832	2	24.4	21.2
	2	83.643	0.8833	2	24.1	19.5
	1	86.572	0.3990	2	25.5	16.7
Gamma	9.92 ± 283	85.151	0.9984	1	24.8	19.3
Logistic	NA[a]	85.151	0.9994	1	25.3	22.0
Log-Logit	8.79 ± 922	85.151	0.9995	1	25.1	19.4
Probit	NA	85.151	0.9994	1	25.2	22.1
Log-Probit	2.30 ± 76	85.151	0.9995	1	24.1	18.2

[a]NA means that a model statistic cannot or will not be calculated. The gray shaded models did not attain the model selection criteria used for BMDS.

Table B-5. BMD modeling results employing the pooled median of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric

Model	Power	AIC	*p*	Df *p*	BMC_{10}	$BMCL_{10}$
Weibull	12	85.151	1.0000	1	17.8	13.8
Multistage (Weibull Integer Power)	8	83.151	1.0000	2	17.7	16.8
	7	83.151	1.0000	2	17.7	16.6
	6	83.151	1.0000	2	17.6	16.4
	5	83.152	0.9997	2	17.5	16.1
	4	83.160	0.9977	2	17.4	15.7
	3	83.218	0.9833	2	17.3	15.0
	2	83.640	0.8838	2	17.0	13.8
	1	86.572	0.3989	2	18.0	11.8
Gamma	9.82 ± 234	85.151	0.9983	1	17.5	13.6
Logistic	NA[a]	85.151	0.9994	1	17.9	16.1
Log-Logit	8.77 ± 547	85.151	0.9995	1	17.7	13.7
Probit	NA	85.151	0.9994	1	17.8	15.6
Log-Probit	2.30 ± 234	85.151	0.9995	1	17.5	12.9

[a]NA means that a model statistic cannot or will not be calculated. The gray shaded models did not attain the model selection criteria used for BMDS.

Table B-6. BMD modeling results employing the pooled arithmetic mean of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric

Model	Power	AIC	*p*	Df *p*	BMC_{10}	$BMCL_{10}$
Weibull	18	83.151	1.0000	2	52.5	36.7
Multistage (Weibull Integer Power)	8	83.151	1.0000	2	52.0	49.4
	7	83.151	1.0000	2	51.9	48.9
	6	83.151	1.0000	2	51.8	48.2
	5	83.151	1.0000	2	51.5	47.4
	4	83.152	0.9999	2	51.2	46.1
	3	83.158	0.9983	2	50.7	44.0
	2	83.259	0.9733	2	49.7	40.2
	1	84.804	0.6518	2	49.5	32.4
Gamma	6.59 ± 143	85.151	0.9995	1	51.2	36.5
Logistic	NA[a]	85.151	0.9995	1	52.5	47.0
Log-Logit	6.21 ± 502	85.151	0.9994	1	51.7	36.2
Probit	NA	85.151	0.9995	1	52.1	45.4
Log-Probit	1.67 ± 125	85.151	0.9995	1	50.7	33.3

[a]NA means that a model statistic cannot or will not be calculated. The gray shaded models did not attain the model selection criteria used for BMDS.

B.1.3. Selection of POD

For each fitted model, BMDS provided an overall goodness-of-fit test (χ^2) and an AIC value. The goodness-of-fit test is a measure of the model fit based on the log-likelihood at the maximum likelihood estimates for the parameters. Models with χ^2 *p* values ≥ 0.1 were

considered to have adequate fits. The AIC is a measure of the model fit based on the log-likelihood at the maximum likelihood estimates for the parameters. Within the subset of models that exhibit adequate fit, models with lower AIC values are preferred. The "best-fit" model selection criteria are described in detail in EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c). As seen in Tables B-3 through B-6, almost all of the models provide an adequate fit to the data, and for all practical purposes, many of the models provide a nearly perfect fit to the data with virtually indistinguishable values of AIC. Therefore, other criteria must play a role in model selection. Perhaps, most importantly, is judgment about the power or exponent in the model. The simplest situation is that of the multistage model (equivalently, the Weibull model with an integer value for the exponent or power). Only one parameter is to be estimated from the data in the multistage or fixed-power models. In this case, the background response is virtually constrained to be 0. If one assumes that sensitization to Pt exposure is a strict threshold phenomenon, then the highest possible power provides the best approximation to a jump from no response below the threshold concentration to a positive response above the threshold. This is unlikely to be the case, however, and would probably be rejected if there were more dose groups between the low Pt exposure and high Pt exposure groups (discussed previously as a consequence of so-called exposure measurement error). An alternative is to choose the smoothest curve from no response to response that still provides a near-perfect fit to the data. Among all such possibilities, the models with a perfect *p* value (to within 4 decimal places) are shown in the above tables highlighted in yellow, and the resulting $BMCL_{10}$ values from these models are presented below. No additional information exists on which to base a choice of the best model.

- The pooled geometric mean air Pt with $BMCL_{10}$ = 21.0 ng Pt/m^3 in Table B-3, using a multistage (monomial or single term only) model of degree 5.

- The mid-median air Pt for 1992 and 1993 with $BMCL_{10}$ = 23.2 ng Pt/m^3 in Table B-4 using a multistage (monomial or single term only) model of degree 6.

- The median of pooled or combined air Pt from 1992 and 1993 with $BMCL_{10}$ = 16.4 ng Pt/m^3 in Table B-5 using a multistage (monomial or single term only) model of degree 6.

- The arithmetic mean of pooled or combined air Pt from 1992 and 1993 with $BMCL_{10}$ = 47.4 ng Pt/m^3 in Table B-6 using a multistage (monomial or single term only) model of degree 5.

- The $BMCL_{10}$ values from these models presented above are consistent with the choice of a $NOAEL_{ADJ}$ as a POD; however, as noted in Section 5.2.2. *Methods of Analysis–*

Including Models (PBPK, BMD, etc.), BMD modeling is not recommended when data sets do not contain at least two non-zero response levels.

B.2. INSENSITIVITY TO BMDS MODEL IN FITTING THE INCIDENCE OF POSITIVE SKIN PRICK TESTS FOR Pt IN CATALYST WORKERS USING DIFFERENT Pt DOSE METRICS

The incidence data do not allow selection for a unique best model. The models shown below demonstrate that the standard multistage monomial (using only a single polynomial term) can provide a virtually perfect fit to the data, within a relatively small range of BMDs and benchmark dose, lower 95% confidence limits (BMDLs) across these best-fitting models. We show the BMDS output for the lowest-order multistage model at which no further improvement in model fitting seems possible (Figure B-1).

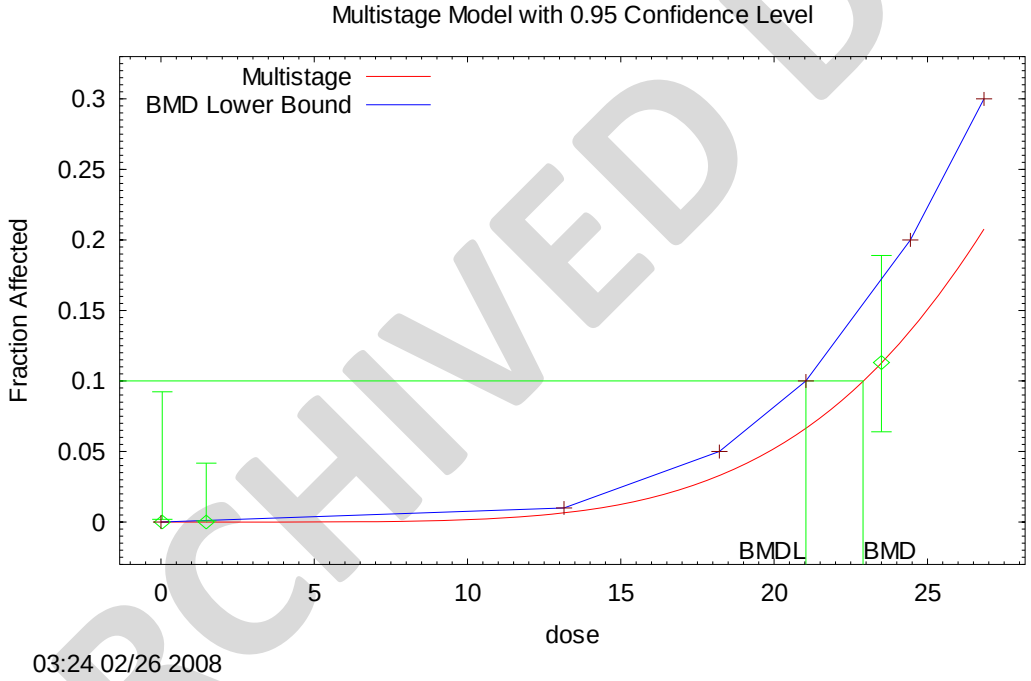

Figure B-1. BMD modeling results employing the pooled geometric mean of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric to support results Table B-3.

```
=================================================================
       Multistage Model. (Version: 2.5;  Date: 10/17/2005)
       Input Data File: U:\IRIS\PLATINUM\MERGET2000.(d)
       Gnuplot Plotting File:  U:\IRIS\PLATINUM\MERGET2000.plt
                                    Tue Feb 26 03:24:38 2008
=================================================================

 SPT POSITIVE GEOMETRIC MEANS PT MULTI STAGE MODEL  DEG 5
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Observation # < parameter # for Multistage model.
   The form of the probability function is:
```

```
   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5-beta6*dose^6-beta7*dose^7-beta8*dose^8)]

   The parameter betas are not restricted


   Dependent variable = SPT
   Independent variable = GEOMMEAN

   User specifies the following parameters:
         Beta(1) =          0
         Beta(2) =          0
         Beta(3) =          0
         Beta(4) =          0
         Beta(6) =          0
         Beta(7) =          0
         Beta(8) =          0


 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 7
 Degree of polynomial = 8


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                 User Inputs Initial Parameter Values
                    Background =            0
                       Beta(1) =            1   Specified
                       Beta(2) =            1   Specified
                       Beta(3) =            1   Specified
                       Beta(4) =            1   Specified
                       Beta(5) =            0
                       Beta(6) =            1   Specified
                       Beta(7) =            1   Specified
                       Beta(8) =            1   Specified


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
-Beta(3)    -Beta(4)    -Beta(6)    -Beta(7)    -Beta(8)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(5)

   Beta(5)           1
```

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Beta(5)	1.67377e-008	1.38153e-008	-1.03398e-008	4.38152e-008

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5756	3			
Fitted model	-40.5756	1	2.6385e-005	2	1
Reduced model	-52.3129	1	23.4746	2	<.0001

AIC: 83.1513

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
23.5000	0.1130	13.000	13	115	-0.000
1.4800	0.0000	0.000	0	111	-0.004
0.0460	0.0000	0.000	0	48	-0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 22.8979

BMDL = 21.0349

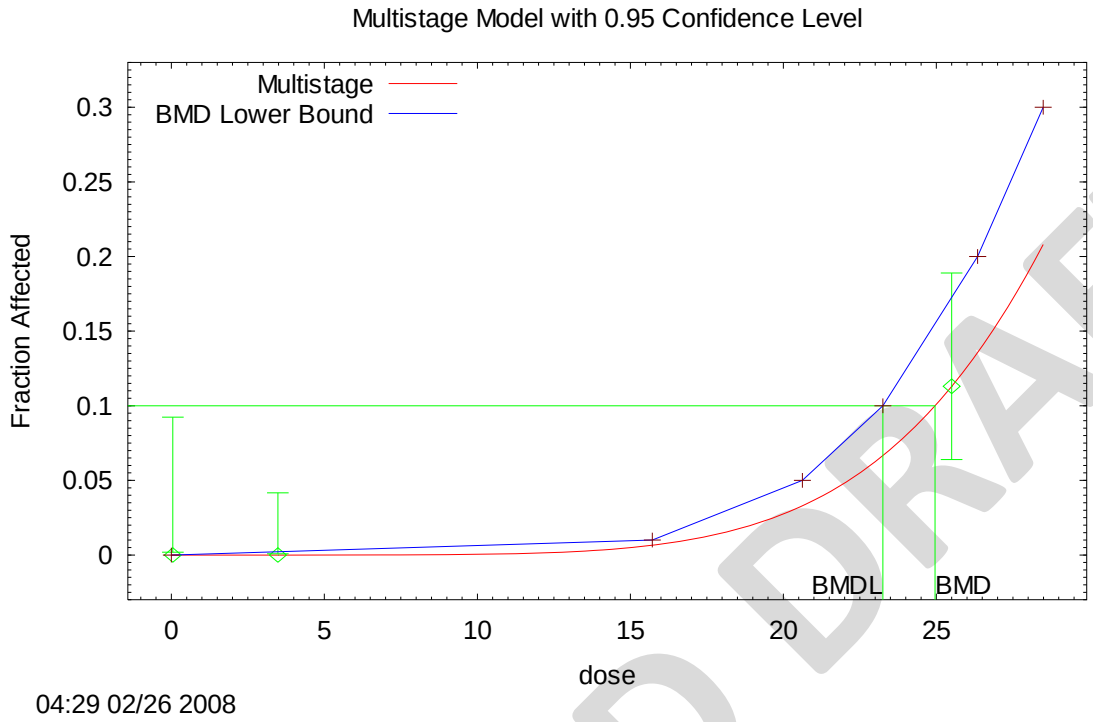

Figure B-2. BMD modeling results employing the mid-median of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric to support Table B-4.

```
 ========================================================================
        Multistage Model. (Version: 2.5;  Date: 10/17/2005)
        Input Data File: U:\IRIS\PLATINUM\MERGET2000.(d)
        Gnuplot Plotting File:  U:\IRIS\PLATINUM\MERGET2000.plt
                                        Tue Feb 26 04:29:56 2008
 ========================================================================

 SPT POSITIVE MID-MEDIANS PT  MULTISTAGE MODEL DEG 6
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Observation # < parameter # for Multistage model.
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5-beta6*dose^6-beta7*dose^7-beta8*dose^8)]

   The parameter betas are not restricted


   Dependent variable = SPT
   Independent variable = MIDMEDIAN

   User specifies the following parameters:
         Beta(1) =          0
         Beta(2) =          0
         Beta(3) =          0
         Beta(4) =          0
```

```
        Beta(5) =          0
        Beta(7) =          0
        Beta(8) =          0


 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 7
 Degree of polynomial = 8


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                User Inputs Initial Parameter Values
                    Background =            0
                       Beta(1) =            1   Specified
                       Beta(2) =            1   Specified
                       Beta(3) =            1   Specified
                       Beta(4) =            1   Specified
                       Beta(5) =            1   Specified
                       Beta(6) =            0
                       Beta(7) =            1   Specified
                       Beta(8) =            1   Specified


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
-Beta(3)    -Beta(4)    -Beta(5)    -Beta(7)    -Beta(8)
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              Beta(6)

   Beta(6)         1



                              Parameter Estimates

                                                        95.0% Wald
Confidence Interval
     Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
    Background                0               NA
       Beta(6)     4.36306e-010     3.60129e-010       -2.69534e-010
1.14215e-009

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-40.5756	3			
Fitted model	-40.5757	1	0.000172036	2	0.9999
Reduced model	-52.3129	1	23.4746	2	<.0001

AIC: 83.1514

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
25.5000	0.1130	13.000	13	115	0.000
3.4800	0.0000	0.000	0	111	-0.009
0.0480	0.0000	0.000	0	48	-0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 24.9544

BMDL = 23.2507

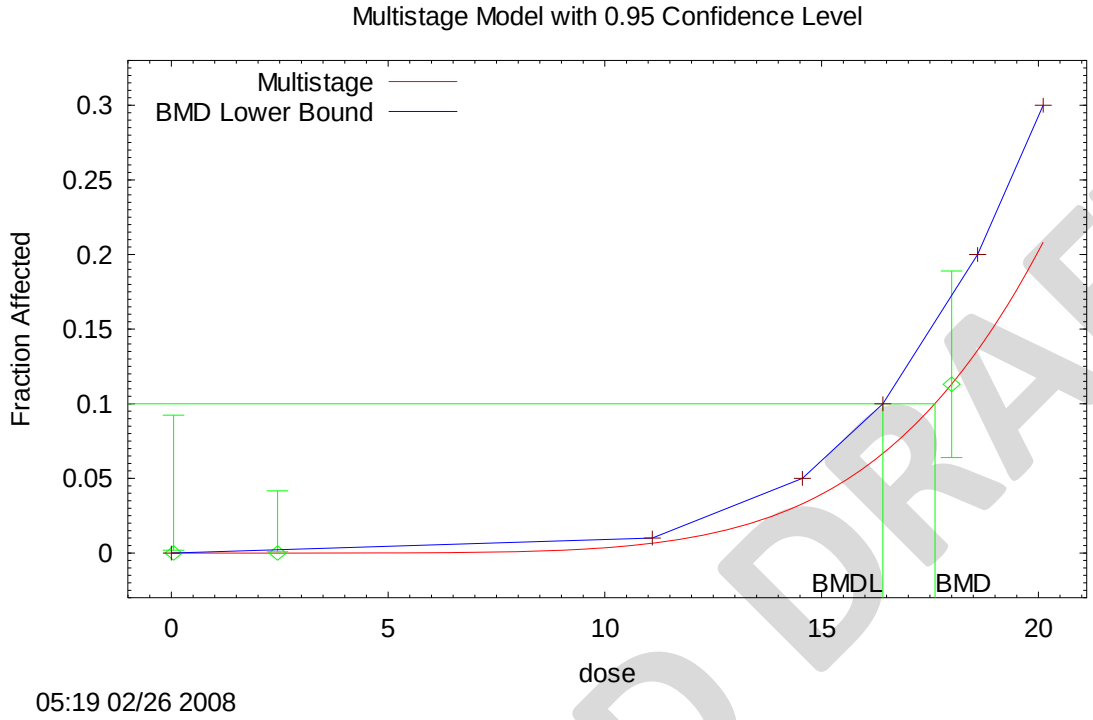

Figure B-3. BMD modeling results employing the pooled median of 1992 and 1993 stationary air monitoring data of soluble Pt as an exposure metric to support Table B-5.

```
 ================================================================
        Multistage Model. (Version: 2.5;  Date: 10/17/2005)
        Input Data File: U:\IRIS\PLATINUM\MERGET2000.(d)
        Gnuplot Plotting File:  U:\IRIS\PLATINUM\MERGET2000.plt
                                        Tue Feb 26 05:19:16 2008
 ================================================================

 SPT POSITIVE MEDIAN PT  MULTISTAGE MODEL DEG 6
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

Observation # < parameter # for Multistage model.
   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2-beta3*dose^3-beta4*dose^4-
beta5*dose^5-beta6*dose^6-beta7*dose^7-beta8*dose^8)]

   The parameter betas are not restricted

  Dependent variable = SPT
   Independent variable = MEDIAN

   User specifies the following parameters:
         Beta(1) =          0
         Beta(2) =          0
         Beta(3) =          0
         Beta(4) =          0
         Beta(5) =          0
```

```
        Beta(7) =          0
        Beta(8) =          0


 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 9
 Total number of specified parameters = 7
 Degree of polynomial = 8


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                 User Inputs Initial Parameter Values
                     Background =            0
                        Beta(1) =            1   Specified
                        Beta(2) =            1   Specified
                        Beta(3) =            1   Specified
                        Beta(4) =            1   Specified
                        Beta(5) =            1   Specified
                        Beta(6) =            0
                        Beta(7) =            1   Specified
                        Beta(8) =            1   Specified


          Asymptotic Correlation Matrix of Parameter Estimates

          ( *** The model parameter(s)  -Background    -Beta(1)    -Beta(2)
-Beta(3)    -Beta(4)    -Beta(5)    -Beta(7)    -Beta(8)
                have been estimated at a boundary point, or have been
specified by the user,
                and do not appear in the correlation matrix )

              Beta(6)

   Beta(6)         1


                                Parameter Estimates

                                                          95.0% Wald
Confidence Interval
     Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
     Background                0               NA
       Beta(6)     3.52693e-009     2.91115e-009       -2.17881e-009
9.23267e-009

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table
```

```
       Model      Log(likelihood)  # Param's Deviance  Test d.f.   P-value
     Full model         -40.5756         3
   Fitted model         -40.5757         1   0.000169335      2
0.9999
  Reduced model         -52.3129         1       23.4746      2         <.0001

           AIC:          83.1514


                                  Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size          Residual
  ---------------------------------------------------------------------------
   18.0000     0.1130        13.000        13         115           0.000
    2.4500     0.0000         0.000         0         111          -0.009
    0.0500     0.0000         0.000         0          48          -0.000

 Chi^2 = 0.00      d.f. = 2        P-value = 1.0000


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        17.6149

            BMDL =        16.4122
```