Precious Metals Consortium

Precious Metals & Rhenium Consortium

PGM Tox Experts Meeting

19 April 2016 | MCC, Brussels

Precious Metals Consortium

1. Welcome and introduction

1.1 Confidentiality and Competition law

1.2 Tour-de-table and apologies

DO	DON'T
Application of competition law	
Art. 101 and 102 TFEU may be applicable to the conclusion of any preliminary agreement and activities of any preliminary phase.	Don't assume that conflicts with competition law are excluded simply by the fact that the Agreement complies with the provisions of the REACH Regulation.
Consultation in Matters of Competition Law	
Consult an in-house legal expert or the compliance officer of your company or an external lawyer whenever there are uncertainties respecting compliance with competition law. Stop all meetings/discussions which are not in compliance with these Compliance Guidelines until a legal expert has been involved.	Don't assume that these Compliance Guidelines deal with all competition law issues exhaustively. Basically, compliance with Art. 101 and 102 TFEU can be determined only on the basis of market impact in each individual case. These Compliance Guidelines may therefore be regarded only as a means of providing general conduct recommendations.
Activities in any preliminary phase and at any other stage of operation of the Consortium	
Restrict cooperation within the scope of the preliminary phase to the initially defined goals and purposes of the cooperation.	Pursuant to Art. 101 and 102 TFEU, activities which have the object of the effect of preventing, restricting and/or distorting competition are prohibited within the scope of this Agreement, including: - Coming to agreement, including arrangements or collusions, about prices, markets and customers (see Art. 101 paragraph 1 a)-e) TFEU); - Joint boycotting of other companies; - The unjustified unequal treatment of trade partners; - The abusive exploitation of a dominating market position.
Exchange of Confidential Information	
Involve a Trustee for the exchange of Confidential Information.	The exchange of Information concerning market behaviour and having the object or the effect of preventing, restricting and/or distorting competition is inadmissible; in particular, this relates to : - Production capacities; - Productions or sales volumes; - Import volumes; - Market shares; - Price policy; - Distribution and marketing terms; - Marketing strategies; - Information regarding the relationship with suppliers.
Documentation on Cooperation	
Keep minutes of all meetings which detail the subject of the meeting. In case of uncertainty, have the contents of the minutes reviewed by an external legal expert prior to sending them to all parties of the Agreement. Stop all meetings which are not in compliance with these Guidelines until a legal expert has been involved.	

1.3 Approval of the agenda

1. Welcome and introduction
2. PGM testing programme
    - 2.1.PGM phys.-chem. Testing
    - 2.2 PGM ecotox testing (Karstedt: Hydrolysis & further ecotox testing, HHPA-2AE)
    - 2.3 PGM HH testing (Karstedt and HHPA-2AE, RuCl3 and TetradoRu, Rh(III) genotox classification)
3. PNEC and DNEL derivation
    - 3.1 PNEC derivation
    - 3.2 DNEL derivation (Pd DNELs, Pd and Pt genotox, ClPt: update, Other Pt DNELs, Read across approach)
4. Occupational Monitoring project: status
5. AOB, next meetings/calls and closing remarks

Precious Metals Consortium

3. PGM Testing Programme

3.1 Phys-Chem testing – outstanding tests of new solids

- Following substance identity discussions, some PGMs that were going to be registered as solutions will now be registered as solids
  - Solutions will be considered to be mixtures
- Additional phys-chem tests required for solid form for the following substances:
  - Palladium dinitrate (melting point, boiling point, flammability, self-ignition temperature, oxidising properties (solid), particle size)
  - Tetraamminepalladium(2+) dihydroxide (Melting point, boiling point, density, flammability, self-ignition temperature, particle size)
  - Tetramminepalladium(2+) diacetate (Melting point, boiling point, density, flammability, self-ignition temperature, particle size)
  - Platinum dinitrate (Melting point, boiling point, density, flammability, explosive properties (possibly required), self-ignition temperature, oxidising properties, particle size)
  - Rhodium tris(2-ethylhexanoate) (Melting point, boiling point, density, flammability, self-ignition temperature, particle size)
  - Palladium sulphate (density)
  - Diammineplatinum (II) nitrite – Explosive when dry, testing of solid not possible?
- Quotes received from BAM, Siemens and Fraunhofer

Platinum Group Metals Ecotoxicity Testing

April 2016

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Palladium	**Diamminedichlororpalladium (DDP)**	Algae Inhibition of Growth (72 hours)	Completed April 2012 [Fraunhofer]	EC50 Yield = 4.03 µg/L (2.03 as Pd) EC50 Growth Rate = 5.88 µg/L (2.96 as Pd) NOEC Yield & Growth Rate = 2.64 µg/L (1.33 as Pd)	Most sensitive taxonomic group Lowest acute EC50 and long-term NOEC
		Daphnia Immobility (48 hours)	Completed June 2012 [Fraunhofer]	EC50 = 69.91 µg/L (35.19 as Pd)	-
		Fish Mortality (96 hours)	Completed June 2012 [Fraunhofer]	EC50 = 306 µg/L (154 as Pd)	-
		ASRIT (3 hours)	Completed March 2012 [Laus]	EC50 = 61 mg/L (30.5 as Pd) NOEC = 18 mg/L (9 as Pd)	-
		Daphnia Reproduction (21 days)	Completed July 2014 [Fraunhofer]	NOEC = >28.39 µg/L (>14.2 as Pd)	Definitive test concentrations selected based on slight (equivocal) effect at 10 µg/L in range-finder. Analysis proved challenging - ammonia stabilisation and Cs std eventually successful Considerable loss of test material over 3 day renewal frequency – results based on mean measured concentrations
		Chironomid Sediment Toxicity (28 days)	Completed November 2013 [Fraunhofer]	NOEC = >60 µg/L (>30 as Pd)	60 µg/L was the maximum concentration that could be maintained in sediment .
	Palladium di (4-oxopent-2-en-2-oate) (PdAcAc)	*Daphnia* Immobility (48 hours)	Completed July 2014 [Fraunhofer]	EC50 = 217 µg/L (76 as Pd)	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Platinum	**Dihydrogen hexahydroxyplatinate (HHPA)**	Algae Inhibition of Growth (72 hours)	Completed September 2014 [Fraunhofer]	EC50 Yield = 3455 µg/L (2240 as Pt) EC50 Growth Rate = 10200 µg/L (6630 as Pt) NOEC Yield = 946 µg/L (613 as Pt) NOEC Growth Rate = 1760 µg/L (1140 as Pt)	Some issues with recovery of test substance, in range-finder . Additional stability trials conducted. Acceptable recoveries obtained in definitive test.
		Daphnia Immobility (48 hours)	Completed August 2014 [Fraunhofer]	EC50 = 742 µg/L (481 as Pt)	Some issues with recovery of test substance, in range-finder . Additional stability trials conducted. Acceptable recoveries obtained in definitive test with fresh solution but rapid loss of test material over 24 hours. Only 30% effect at highest test concentration therefore EC50 is extrapolated. Results of RF suggested 40% effect at 68 µg/L Pt but only 30% effect at 481 µg/L Pt in definitive (geometric mean concentrations).
		ASRIT (3 hours)	Completed December 2014 [Laus]	EC50 = >1000 mg/L NOEC = 320-1000 mg/L	-
	Diammonium hexachloroplatinate (AHCPt)	*Daphnia* Immobility (48 hours)	Completed September 2014 [Fraunhofer]	EC50 = 284 µg/L (108 as Pt)	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Platinum (cont.)	**Dihydrogen hexahydroxyplatinate with 2-aminoethanol (HHPA-2AE)**	*Daphnia* Immobility (48 hours)	In Progress [Fraunhofer]	-	The two compounds separate in water and therefore the same issues as testing HHPA alone arise, with good recoveries on preparation (if stirred for 1-2 hours only in stock) and then loss of Pt from solution over test duration. Definitive tests will therefore be conducted as semi-static tests (stocks stirred for 1 hour) with filtration to allow mean measured concentrations of soluble Pt to be used in results (alongside measured 2-AE concentrations).
		Fish Mortality (96 hours)	In Progress [Fraunhofer]	-	
		Algae Inhibition of growth (72 hours)	In Progress [Fraunhofer]	-	
		ASRIT (3 hours)	Complete [Laus]	3hr EC50: Without ATU = 1100 mg/L With ATU = 1400 mg/L.	
	Hexachloroplatinic Acid (HCPA)	ASRIT (3 hours)	Complete [Laus]	3 hr EC50: Without ATU = 104 mg/L With ATU = 83 mg/L	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Platinum (cont.)	**Karstedt Concentrate**	*Daphnia* Immobility (48 hours)	Not yet approved	-	-
		Fish Mortality (96 hours)	Not yet approved	-	
		Algae Inhibition of growth (72 hours)	Not yet approved	-	
		ASRIT (3 hours)	Not yet approved	-	
		Hydrolysis	Not yet approved	-	

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Ruthenium	**Tetraammonium decachloro-mu-oxodiruthenate (TERTADO Ru)**	Algae Inhibition of Growth (72 hours)	Testing Complete Report in draft	EC50 (Growth rate) = 0.37 mg/L EC10 (Growth rate) = 0.018 mg/L NOEC (Growth rate) = 0.022 mg/L	Recovery 80-90% at test start, dropping to 40-80% at test end. Toxicity values based on mean measured concentrations.
		Daphnia Immobility (48 hours)	Testing Complete (awaiting chemical analysis) Report in draft	-	Range-finder complete: no effects at 0.05, 0.5 & 5 mg/L. Recovery 40-70% over 48 hours.
		Fish Mortality (96 hours)	Complete	No effects up to maximum exposure concentration (nominally 100 mg/L). EC50/ NOEC = > 73.6 mg/L	50-60% losses over 48 hour renewal period (semi-static test). Toxicity values based on time weighted measured concentrations.
		ASRIT (3 hours)	Complete	EC50 = 740 mg/L (with ATU) & 500 mg/L (without ATU)	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Ruthenium (cont)	**Ruthenium trichloride**	Algae Inhibition of Growth (72 hours)	In Progress [Fraunhofer]	-	Results of RF suggest effects at highest concentration only (approx 10% based on growth rate). Issues with solubility and maintenance of test concentrations during test. Discussion with manufacturer and PMRC suggests test item is highly soluble but hydrolyses rapidly to insoluble Ru(OH)3 and RuO2 in water. Range-finderswill be repeated. All samples to be filtered. Test solutions to be prepared directly (no stock solutions) and maintain a low pH to reduce hydrolysis rate.
		Fish Mortality (96 hours)	In Progress [Fraunhofer]	-	
		ASRIT (3 hours)	Complete	EC50 (without ATU) = 530 mg/L, EC50 (with ATU) = 330 mg/L	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Progress April 2016

Metal	Compound	Test	Progress	Result	Notes
Rhodium	**Diammonium sodium hexakis (nitrito-N) rhodate (Rh Nitrite)**	*Daphnia* Immobility (48 hours)	Complete	EC50 = 81.3 mg/L	-
		Algae Inhibition of Growth (72 hours)	Complete	EC50 (Growth rate) = 4.5 mg/L EC10 (Growth rate) = 0.31 mg/L NOEC (Growth rate) = <0.3 mg/L	-
		ASRIT (3 hours)	Complete	EC50 = >1000 mg/L	-

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: HHPA-2AE

- The two compounds separate in water and therefore the same issues as testing HHPA alone arise, with good recoveries on preparation (if stirred for 1-2 hours only in stock) and then loss of Pt from solution over test duration.

- Definitive fish & Daphnia tests will therefore be conducted as semi-static tests (stocks stirred for 1 hour) with filtration to allow mean measured concentrations of soluble Pt to be used in results (alongside measured 2-AE concentrations).

- Algae
  - Definitive test: Biology complete; Some analytical work still to complete.
  - Estimated completion in May/June 2016.

- Daphnia
  - Definitive test scheduled for April 2016
  - Estimated completion in June/ July 2016

- Fish
  - Definitive test scheduled for April 2016
  - Estimated completion in June/ July 2016

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Karstedt Concentrate

- Substance is complex (Pt siloxane) and Pt
- Known to hydrolyse relatively quickly in water at neutral pH (a few hours) & extremely quickly as pH becomes (even slightly) acidic or alkaline (minutes).
  - Initial hydrolysis to Pt and organic ligand (siloxane)
  - Organic ligand then suspected to hydrolyse further
- Analysis of complex not possible, but Fraunhofer have now developed method for detection of organic ligand.
- Preliminary hydrolysis testing conducted (4.3mg/L test item, pH 7, 96 hours)
  - Reducing concentrations of detectable Pt and organic ligand over time
  - Both still detectable after 96 hours (approx. 270 ug/L Pt & 20 ug/L ligand)
- Primary ligand still detectable over period equivalent to acute ecotox tests
- May cause toxicity (in addition to Pt)
- **Ecotox testing may be required (+ full GLP hydrolysis test)**
- If testing commenced asap (realistically May 2016 at earliest), estimated completion of testing in autumn 2016

3.2 PGM Ecotox testing

Ecotoxicity Testing Programme: Ruthenium Trichloride

- Results of RFs suggest issues with solubility and maintenance of test concentrations during test
- Discussion with manufacturer and PMRC suggests test item is highly soluble but hydrolyses rapidly to insoluble $Ru(OH)_3$ and RuO_2 in water. RuO_2 will also bind readily to surfaces

- Algae
  - Range-finder will be repeated. All samples to be filtered. Test solutions to be prepared directly (no stock solutions) and maintain a low pH to reduce hydrolysis rate.

- Fish
  - Range-finder repeated. All samples filtered. Test solutions prepared directly (no stock solutions) and maintain a low pH to reduce hydrolysis rate.
  - No effects.
  - pH of dilution water used = 6, but higher concentrations caused a marked further reduction in pH (to 2-3) which was too low to allow exposure of fish.
  - pH of these concentrations carefully increased back to 6, and remained near to 6 throughout test. However, on adjustment, some precipitation was observed (i.e. hydrolysis and precipitation of insoluble hydrolysis products). Filtered analytical samples clear.
  - Ru precipitates faster with higher concentrations. However, we still do not know the maximum achievable concentration, which is either between 1 mg/L and 10 mg/L, or between 10 mg/L and 100 mg/L.
  - Based on these observations, there are two suggestion for the further procedure:
  - 1. Another pre-test with two concentrations (5.0 and 50.0 mg test item/L) in order to determine the maximum achievable concentration of Ru in the test solutions, applying the same procedure as before. This pre-test would be performed without fish and only for two days. This pre-test would result in 4 further samples for analysis.
  - 2. Perform the definite test as a limit test with a concentration of 10 mg test item/L, as this concentration would lead to a maximum ruthenium concentration (as known so far).

3.2 PGM Ecotox testing – discussion

- Karstedt concentrate
  - Propose to proceed with ecotox tests
  - Do full hydrolysis test
- RuCl3
  - Option 1: perform another pre-test at 5.0 and 50.0 mg test item/L in order to determine the maximum achievable Ru concentration in the test solutions (without fish, 2 days)
  - Option 2: Perform the definite test as a limit test with a concentration of 10 mg test item/L

3.2 PGM Ecotox testing – proposed changes C&L

- Availability chronic Daphnia and algae data for DDP allowed recalculating M-factors for Pd substances
  - Diamminedichloropalladium: chronic M factor 100 Ÿ 10
  - Palladium dichloride: chronic M factor 100 Ÿ 10
  - Disodium tetrachloropalladate: chronic M factor 100 Ÿ 10

PGM Tox Experts Group Meeting

Brussels
19 April 2016

Karstedt Concentrate

Test	CRO	Status
Skin irritation in vitro Epiderm - OECD 439	LPT	Starts Apr 16
Eye irritation in vitro - OECD 437	LPT	Starts Apr 16
Local Lymph Node Assay - OECD 442B	LPT	Starts Apr 16
In vitro mammalian cell micronucleus test (human lymphocytes) ï OECD 487	Covance	Starts Apr 16
In vitro gene mutation in mammalian cells (hrpt assay in mouse lymphoma cells) ï OECD 476	Covance	Dependent on above
Acute oral toxicity Up-and-down procedure - OECD 425	LPT	Starts May 16
Acute dermal toxicity - OECD 402	LPT	Dependent on above
Preliminary repeat dose toxicity	LPT	Starts May 16
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test	LPT	Starts Jul 16

Initial formulation analysis demonstrates that Karstedt concentrate is stable in corn oil at 1 and 100 mg/mL for 7 days.

PMC note: could not wait for hydrolysis data, evaluated corn oil as vehicle

Dihydrogen hexahydroxyplatinate ï 2AE

All studies at LPT

Test	Result	Status
Skin irritation in vitro Epiderm - OECD 439	Irritant Cat 2	Complete
Eye irritation in vitro - OECD 437	No prediction*	Complete
Local Lymph Node Assay - OECD 442B	Negative	Complete
Skin corrosion in vitro. Epiderm OECD 431	Corrosive Cat 1B/1C	Reporting
Preliminary repeat dose toxicity		Starts Jun 16
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test		Starts Jul 16

* Above cut-off for no classification and below cut-off for Cat 1

Initial formulation analysis demonstrates that HHPA-2AE is stable in corn oil at 125 mg/mL for 7 days.

PMC note: Classify (not label!) as causing serious eye damage, based on results of skin sorr. Cat. 1B/C

Ruthenium Chloride

Test	CRO	Result	Status
GLP Ames reverse mutation assay in 5 strains - OECD 471	Covance	Negative	Complete
In vitro mammalian cell micronucleus test (human lymphocytes) ï OECD 487	Covance	Negative	Complete
In vitro gene mutation in mammalian cells (hrpt assay in mouse lymphoma cells) ï OECD 476	Covance		Ongoing
Preliminary repeat dose toxicity	CiToxLAB		Starts May 16
28 day repeated dose toxicity (dietary) with recovery - OECD 407	CiToxLAB		Starts Jul 16
Reproduction/developmental toxicity screening test (dietary route) - OECD 421	CiToxLAB		Starts Aug 16

Preliminary analytical work has demonstrated stability in diet at 10,000 ppm For 14 days

Tetraammonium decachloro-mu-oxodiruthenate

Test	CRO	Result	Status
GLP Ames reverse mutation assay in 5 strains - OECD471	Covance	Negative	Complete
In vitro mammalian cell micronucleus test (human lymphocytes) ï OECD 487	Covance	Negative	Complete
In vitro gene mutation in mammalian cells (hrpt assay in mouse lymphoma cells) ï OECD 476	Covance	Negative	Reporting
Local Lymph node assay	CiToxLAB	Sensitiser	Complete
Acute oral toxicity ï OECD 425	LPT	3110 mg/kg	Reporting
Preliminary repeat dose toxicity	LPT	* see next slide	Reporting
Repeated dose oral toxicity ï OECD TG407	LPT	Decision on study types to be made	
Reproduction/developmental toxicity screening test ï OECD TG421	LPT		
Combined repeat dose oral toxicity with reproduction/developmental toxicity screening test ï OECD TG422	LPT		

Stability in corn oil at 1 and 100 mg/mL demonstrated.

PMC note: EC3 30.9% w/v

Tetraammonium decachloro-mu-oxodiruthenate

14 day preliminary repeat dose oral in rats:

- Groups of 5/sex at 500, 750 and 1000 mg/kg bw/day in corn oil
- Dark faeces at 1000 mg/kg
- Dose-related reduction in body weight gain, significant in males at 750 and 1000
- Lower food consumption in males at 1000 mg/kg week 1
- Lower absolute and relative liver weights males all groups, not dose-related

	Male		Female	
Dose (mg/kg)	**Body weight (g)**	**Difference**	**Body weight (g)**	**Difference**
0	311.90		223.66	
500	290.76	-7.6%	219.08	-2.0%
750	280.50*	-10.1%	214.36	-4.2%
1000	266.76**	-14.5%	209 6	-6.3%

3.3 PGM HH testing

- TetradoRu - decide on
  - OPTION 1
    - -Repeated dose oral toxicity – OECD TG407 PLUS
    - -Reproduction/developmental toxicity screening test – OECD TG421
  - OPTION 2
    - Combined repeat dose oral toxicity with reproduction/developmental toxicity screening test – OECD TG422

3.3 PGM HH testing – proposed changes C&L

- Pd(OH)2
  - not classified Ÿ Acute tox 4 (oral), Eye Dam. 1, Skin Sens. 1.
  - **N.B.:** Now exposure scenarios needed for human health
- PdCl2
  - Additional classification as Acute tox 4 (oral),
- Na2PdCl4
  - Additional classification as Skin sens 1A,
- Diammonium hexachloropalladate
  - Additional classification as Acute tox 4 (dermal)
- Dipotassium hexachloropalladate
  - Additional classification as Acute tox 4 (dermal)

3.3 PGM HH testing – Rh(III) genotox classification

- Rh (III) genotox testing – overview
  - Water soluble compounds:
    - RhCl3: mutagenic activity in 1 *in vivo* and 3 *in vitro* assays Ŷ decided to classify as Muta2
    - Rh(III) sulphate, Rh(III) nitrate (soluble!), Rh(III) acetate, triammonium hexachlororhodate: positive AMES
  - Relatively water soluble compound: diammonium sodium hexakis(nitrito-N)rhodate ('*Rh nitrite*'): 3 negative *in vitro* assays
    decided to classify as Muta2
  - Water insoluble compound: Rh(III) triiodide: positive AMES
- Decisions PMC members:
  - Classify some Rh(III) compounds
  - RA Muta2 classification to '*relevant soluble Rh(III) compounds in-scope*'
- Information D Boyd (March 2016):
  - Rhodium = 'soft' metal

    - preference for 'soft' ligands such as halides, nitrogen or sulphur ligands

    - no preferential bonds with 'hard' ligands unless thermodyn. stabilized (solution chemistry, polymorisation)
  - **3 groups according to their chemistry:**

    1/ metal, oxides, hydroxides

    2/ RhCl3, RhI3, triammonium hexachlororhodate

    3/ Rh trisulphate, -trinitrate, -acetate and –tris(2-ethylhexanoate)

3.3 PGM HH testing – Rh(III) genotox classification

Å Information D Boyd (March 2016) (continued)

1/ metal, oxides, hydroxides (poor WS)

Neutral to mildly acidic pH: substantially INSOLUBLE (involves sequence of aquated complexes)

Acidic pH : °(hydr)oxide: dissolve (formation chloro-aqua complexes)

° Metal: marginally soluble (~surface oxide/hydroxide)

2/ RhCl3, triammonium hexachlororhodate (high WS), RhI3 (poor WS)

octahedral similar to 'simple' halide? (halogen bridged polymer)

Neutral to mildly acidic pH: cfr water solubility

Acidic pH: likely replacement aqua species by chloro ligands (RhI3 more potent than RhCl3?)

3/ Rh trisulphate, -trinitrate, -acetate (high WS) and –tris(2-ethylhexanoate) (poor WS)

probable all polymeric substances ~ coordination and oxo ligand bridging

Neutral to mildly acidic pH: cfr water solubility

Acidic pH: decomposition expected (substitution by Cl-ligands)

4/ *Rh nitrite* (moderate WS)

Acidic pH: decomposition due to absence of stabilizing excess nitrite (evolving NOx)

3.3 PGM HH testing – Rh(III) genotox classification

Å **Recommendation**:

1/ classify all water soluble Rh(III) compounds as Muta2

Rh sulphate, -trichloride, -nitrate, -acetate, triammonium hexachlororhodate

2/ include testing proposal for *in vivo* genotoxicity testing for Rh nitrite

- Å 3 negative *in vitro* testing
- Å high *in vitro* bioaccessibility data (115% @ gastric (pH 1,2; 2h))
  - Ÿ ECHA rejects TP and accepts 'no classification' (not protective)
  - Ÿ ECHA rejects TP and obliges to classify as muta2 (highest chances)
  - Ÿ ECHA accepts TP to help deciding on muta classification

3/ perform *in vitro* bioaccessibility testing with poorly WS compounds (gastric medium)

Rh tris(2-ethylhexanoate), Rh triiodide, -trioxide, -trihydroxide

- Ÿ 'high' bioaccessibility (expected) – cfr Rh nitrite discussion
- Ÿ 'low' bioaccessibility – consider further *in vitro* testing to confirm inert behaviour

4/ do not classify Rh metal

Precious Metals Consortium

4. PNEC and DNEL Derivation

Status of PNEC derivation

- Palladium substances:
  - PNECs agreed and entered into draft IUCLID files
- Rhodium:
  - Draft PNECs derived and report circulated for review
- Platinum
  - PNECs will be derived following completion of ecotox testing with HHPA-2AE
  - Aim to derive PNECs by 30 June '16
- Ruthenium:
  - PNECs will be derived following completion of ecotox testing with ruthenium trichloride
  - Aim to derive PNECs in July

DNEL (Derived No-Effect Level) approach for substances > 10 tpa

Palladium substances

- Genotoxicity
- Final draft DNELs

Platinum substances

- Genotoxicity/testing proposal
- Chloroplatinate DNELs
- Non-Cl Platinate DNELs

Read-across (RA) approach

Palladates genotoxicity

In vitro gene mutation study in bacteria
Substance-specific (SS) or RA Ames tests OECD 471 – all negative

In vitro cytogenicity in mammalian cells
SS/RA in vitro mammalian cell micronucleus tests OECD 487 - all negative

In vitro gene mutation study in mammalian cells
SS/RA Mouse lymphoma assays (MLA) OECD 476 - all negative

In vivo genotoxicity
Data available (e.g. Mammalian erythrocyte micronucleus OECD 474 on tetraamminepalladium hydrogen carbonate (RA) – negative)

Overview
- complete negative dataset
- no testing/classification

For discussion

- Limitations of existing bacterial mutagenicity database Pd-tetraammines
  - Ames test lack of a strain susceptible to oxidative mutagenesis (e.g. TA102 or E.coli strains)
  - ECHA may request new test (via SONC)

- Proposal
  - Overall weight of evidence robust
  - No need for action at that stage. Suggest to wait if ECHA comes back
  - Be prepared to conduct new Ames test at later stage

Palladium DNELs

10 – 100 tpa

Final draft DNEL reports generated for 11 Pd substances (4 read-across “groups”):

- Diammonium hexachloropalladate
- Dipotassium hexachloropalladate

- Diamminedichloropalladium
- Palladium dichloride
- Dihydrogen tetrachloropalladate
- Disodium tetrachloropalladate

- Palladium dihydroxide
- Palladium dinitrate
- Palladium di(4-oxopent-2-en-2-oate)

- Tetraamminepalladium dichloride
- Tetraamminepalladium diacetate

bibra
toxicology advice
& consulting

Palladium DNELs continued…

No general population exposure -> no DNELs (statement to satisfy IUCLID requirements)

Workers:
Quantitative assessment for systemic $DNEL_{long\text{-}term}$ for inhalation and dermal routes

- calculated from the oral dataset (RD/repro studies available for the "parent" compound in each group)
- REACH guidance regarding appropriate Assessment Factors (AFs) and route-to-route extrapolation (i.e. absorption differences)

No hazard identified for systemic $DNEL_{acute}$ since palladium compounds generally exhibit low acute oral/dermal toxicity, while inhalation is not considered a significant route of exposure

Qualitative assessment for local DNELs

- assess available data (irritation/sensitisation)
- hazard level/banding informs RMMs/OCs
- driven mainly by skin sensitisation potential (i.e. high hazard for strong sensitisers)

Qualitative assessment for hazard for the eyes

Palladium DNELs continued…

Summary of quantitative palladium DNELs

Substance	Systemic long-term hazard (DNEL)	
	Inhalation (mg/m^3)	Dermal (mg/kg bw/day)
Diammonium hexachloropalladate	4.70	1.33
Dipotassium hexachloropalladate	5.27	1.49
Diamminedichloropalladium	17.5	24.9
Palladium dichloride	14.7	4.17
Dihydrogen tetrachloropalladate	20.8	5.89
Disodium tetrachloropalladate	24.4	34.6
Palladium dihydroxide	47.0	66.7
Palladium dinitrate	77.2	21.9
Palladium di(4-oxopent-2-en-2-oate)	25.5	36.2
Tetraamminepalladium dichloride	0.19	0.27
Tetraamminepalladium diacetate	0.26	0.36

PMC comment: many DNELs > nuisance dust limits; ES will assume max. 10 mg/ m3

Palladium DNELs continued…

Summary of qualitative palladium DNELs

Substance	Qualitative hazard conclusion (no threshold derived)						
	Inhalation			Dermal			Eyes
	Systemic acute	Local long-term	Local acute	Systemic acute	Local long-term	Local acute	Local effects
Diammonium hexachloropalladate	-	Medium	Medium	-	Medium	Medium	Medium
Dipotassium hexachloropalladate	-	Medium	Medium	-	Medium	Medium	Medium
Diamminedichloropalladium	-	-	-	-	-	-	Medium
Palladium dichloride	-	High	High	-	High	High	Medium
Dihydrogen tetrachloropalladate	-	Medium	Medium	-	High	High	Medium
Disodium tetrachloropalladate	-	High	High	-	High	High	Low
Palladium dihydroxide	-	Medium	Medium	-	High	High	Medium
Palladium dinitrate	-	Medium	Medium	-	Medium	Medium	Medium
Palladium di(4-oxopent-2-en-2-oate)	-	High	High	-	High	High	Medium
Tetraamminepalladium dichloride	-	Medium	Medium	-	High	High	Low
Tetraamminepalladium diacetate	-	Medium	Medium	-	High	High	Low

- = No hazard identified

Pd DNELs

- Respiratory tract sensitisation
  - Changed hazard conclusions from “High Hazard (no threshold derived)” to “Moderate Hazard” for
    - Palladium dichloride
    - Dihydrogen tetrachloropalladate
    - Disodium tetrachloropalladate
    - Palladium dihydroxide
    - Tetraamminepalladium dichloride
    - Tetraamminepalladium diacetate
    - Palladium di(4-oxopent-2-en-2-oate)
  - Rationale: for skin sensitizers (Category 1A or 1) there is a strong scientific argument to assume that sensitisation of the respiratory tract may also occur following inhalation exposure. As such, suitable OCs/RMMs – to mitigate inhalation exposure – are suggested where a substance is classified as a potent skin sensitiser
  - Note that no classification as respiratory sensitisers is proposed

- Pd di(4-oxopent-2-en-2-oate
  - AF of 4 retained for allometric scaling (not for other substances) to compensate for uncertainty regarding potential effects of the anion (no specific evaluation of the anion was possible)
  - Suggest to revisit at next dossier update

Platinates genotoxicity

- A number of the in vitro genotoxicity assays (assessments for gene mutation, oxidative DNA damage and chromosomal aberration) for platinum compounds have been positive
- Lack of good quality in vivo data impedes robust classification on germ cell mutagenicity

Tetraammineplatinum dinitrate: in vivo data available - negative results (not full guideline/REACH recommended studies)

- Micronucleus OECD 474, Sex-linked recessive lethal test in Drosophila (equivalent to OECD 477) and Bone marrow chromosome aberration test (eq. to OECD 475) all on tetraammineplatinum dichloride (RA)
- Liver unscheduled DNA synthesis (UDS) assay (eq. to OECD 486) on tetraammineplatinum hydrogen carbonate (RA)

However, clear positive evidence exists for cisplatin (and some other platins), but this is expected considering its molecular characteristics and mechanistically is of uncertain predictive value for genotoxic effects of other Pt compounds

Platinates genotoxicity continued…

Do not classify those Pt substances with positive in vitro assays as genotoxic

Include in vivo genotoxicity test proposal(s) on suitable Pt salt(s) in the REACH dossier

- Diammonium hexachloroplatinate
- Dipotassium hexachloroplatinate
- Hexachloroplatinic acid
- Dihydrogen hexahydroxyplatinate

Platinum dinitrate (Waive on basis of technical and scientific non-justification; possibility to use results from dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2) (HHPA) in vivo test)

Following the results of the in vivo genotoxicity testing, need to reconsider

- Mutagenicity classification & labelling
- DNELs vs DMELs
- Hazard banding (RMMs/OCs)

For discussion

- Proposal:
  - not to classify Pt substances as genotoxic at that stage
  - Proposal to submit testing proposals for *in vivo* testing

N.B.: May need further discussions on TP with ECHA on best way forward. Wait for feedback on TP

Chloroplatinate DNELs

10 – 100 tpa

Draft DNEL reports generated for the following chloroplatinates in Q1:

- Diammonium hexachloroplatinate
- Dipotassium hexachloroplatinate
- Hexachloroplatinic acid

Well established reports of respiratory sensitisation with this sub-category (critical difference to Pd DNELs)

Systemic $DNEL_{long\text{-}term}$ initially calculated by analogous method to Pd compounds

- Determined inhalation values higher (>2 orders of magnitude) than the Occupational Exposure Limit (OEL) of 2 µg/m^3 for soluble Pt salts (expressed as Pt metal)
- OEL informs systemic $DNEL_{long\text{-}term}$ for inhalation and dermal routes (non-standard, but more precautionary) after accounting for absorption differences
- Potential for molecular weight extrapolation (i.e. substance specific DNELs)?

Chloroplatinate DNELs

10 – 100 tpa

Key differences from Pd reports
Medium/high hazard identified for systemic $DNEL_{acute}$ since these compounds are classified for Acute toxicity in category 2/3

Inhalation local DNELs

- Classification as respiratory sensitiser 1A necessitates allocation to the high hazard band
- Epidemiology literature (Heederik et al., 2016; Merget et al., 2000) indicates respiratory tract (RT) effects at levels lower than the OEL
- As such, the suitability of the OEL for protecting workers from potential RT sensitisation to be further investigated

DNEL reports to be reviewed and subsequently finalised in the coming weeks

DNELs for non-Cl Platinates

10 – 100 tpa

Draft DNEL reports generated for three non-chloroplatinates in Q1:

- Dihydrogen hexahydroxyplatinate
- Tetraammineplatinum dinitrate
- Platinum dinitrate (UVCB)

Systemic $DNEL_{long\text{-}term}$ approach was similar to the chloroplatinates

Key differences from chloroplatinate reports
Platinum dinitrate

- hazard unknown for systemic $DNEL_{acute}$ since this compound involved waiving of all acute toxicity testing on the basis of a low pH
- Non-sensitising to skin/RT, but skin corrosive -> high hazard band for local DNELs

Dihydrogen hexahydroxyplatinate and tetraammineplatinum dinitrate generally exhibited much “cleaner” profiles (i.e. no hazard identified for majority of qualitative endpoints)

Platinum DNELs

Summary of quantitative platinum DNELs

Substance	Systemic long-term hazard (other toxicological threshold)	
	Inhalation ($\mu g/m^3$)	Dermal (µg/kg bw/day)
Diammonium hexachloroplatinate	2	1.43
Dipotassium hexachloroplatinate	2	1.43
Hexachloroplatinic acid	2	1.43
Dihydrogen hexahydroxyplatinate	2	2.86
Tetraammineplatinum dinitrate	2	2.86
Platinum dinitrate	2	1.43

PMC remark: calculated DNELs >> official OEL (2 ug/m3)
Replaced calculated DNELs by OEL
Official OEL recognized as not protective – s. discussions chloroplatinates

Platinum DNELs continued…

Summary of qualitative platinum DNELs

Substance	Qualitative hazard conclusion (no threshold derived)						
	Inhalation			Dermal			Eyes
	Systemic acute	Local long-term	Local acute	Systemic acute	Local long-term	Local acute	Local effects
Diammonium hexachloroplatinate	Medium	High	High	Medium	Medium	Medium	Medium
Dipotassium hexachloroplatinate	Medium	High	High	Medium	Medium	Medium	Medium
Hexachloroplatinic acid	High	High	High	High	Medium	Medium	Medium
Dihydrogen hexahydroxyplatinate	-	-	-	-	-	-	Low
Tetraammineplatinum dinitrate	-	-	-	-	-	-	-
Platinum dinitrate	Unknown	High	High	Unknown	High	High	Medium

- = No hazard identified
Unknown = Hazard unknown (no further information necessary)

Chloroplatinates – D (M)NELs

- PGM WG conf. call. 3rd Feb. 2016: Discussed options for CPs
  - Options
    - Semi-quantitative approach (= derive a DMEL)
    - Qualitative approach (= “strictly avoid exposure”)
  - WG strongly recommends to follow qualitative approach
    - Uncertainty in deriving potential threshold seen too high
  - Sub-group formed to oversee process
- Sub-group conf. call 23 March 2016
  - Next Steps – Short term
    - Document rationale for REACH dossier
    - Oversee practical implementation in dossier
    - Consider impact on DUs
    - Coordinate with IPA/ STF
      - STF rep. in sub-group
  - Brainstorming session on technical aspects (cfr further in this presentation)

Chloroplatinates – D (M)NELs

- Qualitative approach is best option now, but not sustainable over long-term
- **ECHA screening expected soon after dossier submission**
- Need more sustainable solution long term (semi-quantitative assessment)
- Collaborate with IPA/ STF
  - Working on robust threshold
    - Practical sector guidance
    - Prospective epidemiology study
  - Focus on OEL (not REACH)

Chloroplatinates – D (M)NELs

- How do we justify/ document that no threshold can be determined?
  - No available method at the moment
  - Supporting argument: work ongoing to be able to derive threshold in the future

- Proposed MOE estimation chloroplatinates
  - Need to discuss who will do calculations
  - What threshold level should be used? 100 ng/m3?
  - Need to ensure this is not perceived as contradictory to first bullet

- Plan B
  - Discuss if all uses are sustainable
  - Can all EU producers achieve the target level of 100 ng/m3?

Chloroplatinates – D (M)NELs

Technical considerations: thought starter by Mark Raffray

1. *The main challenge is that "Adequate Control" must be demonstrated as final outcome (note PG 15; Fig 2.2 Decision Tree).*
2. *The necessary pieces of the risk assessment "jigsaw" already exist (with the possible exception of '9' below). To successfully navigate the Qualitative Assessment, the consensus of the registrants is needed on the Assessment inputs/outputs, and then their properly assembly into the CSR (specifically following a REACH Qualitative Assessment format).*
    a. *Working in more detail from Fig 2.2 as a template, preferably at a f2f meeting, is a logical way to progress. Agreement of all necessary inputs, and the identification of any significant difficulties should be an early priority.*
    b. *The included Case Study examples in PG 15 give some pointers, but are not completely relevant to the endpoint of respiratory sensitisation where a DMEL is not available.*
3. *Step 1; Fig 2.2: Decision on what Hazard Banding should be applied – should be an easy first step for the sub-group.*
4. *Step 2; Fig 2.2: Defining (generic) Exposure Scenarios*
    a. *In terms of overall objective, ensure the proper alignment between Sub-Group and EBRC activities. Obtain a picture of EBRC's intended approach at the earliest possible stage.*
    b. *Uses and OC templates will be needed to guide discussions.*
5. *Step 3; Fig 2.2: Estimate Exposure*
    a. *Decide on matching required exposure datasets to Uses and OC, e.g. the IPA epi dataset relates only to certain common handling operations at producer level, and it covers a retrospective period of 10 years (current exposures may have shifted).*
    b. *Then decide whether further measurement or modelled exposure data inputs will be required to cover all the Uses and OC within the dossier.*
    c. *Also consider dermal exposure risk assessment (and consequent specific RMM) as it is clear that respiratory sensitisation potential exists via dermal exposure.*
    d. *It is anticipated that chloroPt DNELs, including systemic dermal DNELs, will be set aside with preference for a Qualitative Assessment with respiratory sensitisation as the leading HH endpoint – but the Sub-Group should discuss/validate.*

Chloroplatinates – D (M)NELs

Technical considerations: thought starter by Mark Raffray (part 2)

6. *Step 4; Fig 2.2: Characterise risk*
   a. *Probably the most difficult area, especially in relation to any residual risk.*
   b. *Which Benchmark Value approach, if any, is most relevant for respiratory sensitisation?*
   c. *If Control Banding chosen as a strategy, then as for other asthmagens in Control Banding schemes, the conclusion will be exposure control to ALARP.*
   d. *In terms of a priority effort for the Sub-Group, this part of the Assessment is likely to be highly dependent on supporting argumentation / expert judgement, plus also objective evidence of a suitable framework of workplace controls. [Guidance states: Statements should be corroborated as much as possible by specific reference to relevant supporting material…..Reference to measured data and to relevant site-specific performance indicators provides strong support for statements that risks are adequately controlled]. The new IPA Guidance document represents a valuable resource in that respect, and also objective evidence of the sector's care standards.*

7. *Step 2; Fig 2.2: RMM associated with Exposure Scenarios*
   a. *Review iterations as necessary until there is confidence about Adequate Control.*
   b. *Obtain consensus on the raft of RMM that are either already in place or achievable by registrants.*
   c. *It is predictable from the hazard_banding:exposure_matrix outcome that containment along with engineering/administrative control approaches will predominate as RMM, but discussions are needed on how to best define and explain in the CSR the mix of these RMM representing Adequate Control.*

8. *Step 4/5; Fig 2.2: Validation that Adequate Control has been demonstrated*
   a. *bibra have suggested to check final risk assessment outcome via Margin of Exposure (MoE) considerations, e.g. ILSI recommended approach – the Sub-Group needs to decide if this is scientifically the correct approach in these specific circumstances (given that it has not routinely been applied to this endpoint).*

9. *Step 4/5; Fig 2.2: Implications for DU using products based on chloroPt salts*
   a. *Some limited non-intermediate (product) uses in EU are known. DU would need to assure same Adequate Control of risk as defined in the final Qualitative Assessment.*
   b. *Discussion with representative DU could be needed.*
   c. *Exposure datasets for such DU are sparse / have been inferred or read-across rather than measured – this may not be tolerable for a high hazard band situation.*

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4. Occupational Monitoring Project - Status

4. Occupational Monitoring Project

- Project agreed during December '15 GA meeting
  - Large number of REACH registrations <2018
  - DNELs expected to be (relatively) low
  - Limited n° of exposure data available
- AIM = collect/gather exposure data at representative workplaces of PGM Industry
- Timing: finalise <end 2016
- Metals under scope = as wide as possible (Rh, Ru, Pt, Pd…)
- EBRC contracted
- So far:
  - Kick-of meeting 18 February in Bxl
  - Participating companies: BASF, Chafner, Chimet, Heraeus, Johnson Matthey, Umicore, Vale
  - Engagement for sharing exposure data and/or site visits
  - 4 site visits scheduled so far (13-14 April and 11-12 May)
- Next steps…cfr proposed timing

4. Occupational Monitoring Project – proposed timing

Action	By whom	Duration	Time
Agree on date for site visit	Companies / EBRC	1 month	Mid March 2016
Easter break	*All*		
Perform site visit	Companies / EBRC (/EPMF)	2 weeks	Mid April 2016
Draft site visit report	EBRC	2 weeks	End April 2016
Revise / approve site visit report	Companies	1 month	End May 2016
Develop data submission form	EBRC	1 month	End June 2016
Summer break	*All*		
Submit monitoring data	Companies	1 month	Mid Aug 2016
Generate database	EBRC	2 weeks	End Aug 2016
Conduct sampling	Sampling institute / Companies	2 weeks	Mid Sep 2016
Sample analysis & drafting report	Sampling institute / EBRC	1.5 month	End Oct 2016
Finalisation of database	EBRC	2 weeks	Mid Nov 2016

ONGOING

4. Occupational Monitoring Project

- Discussion point: Occupational monitoring via inhalable fraction and/or respirable fraction?

  If relevant from toxicological point of view, measuring both fractions might advisable considering current experiences of e.g. Ni consortium.

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5. AOB, Next meeting(s) and closing remarks

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THANK YOU

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