PMC – PGM Tox Experts Group Meeting

24 MARCH 2015

Welcome and introduction

DAVE BOYD

Welcome and introduction

Confidentiality and Competition Law

Tour de table and apologies

Approval of the Agenda

Approval of the minutes of the last meetings (9 Nov 2014) and status of action points

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.	

Approval of the agenda

1. Welcome and introduction
2. Substance identification and sameness of PGMs
3. PGM testing programme
4. Current status of PNEC and DNEL refinement
5. CLP update/ CLP notifications
6. Project Planning
7. AOB, next meetings/calls and closing remarks

Actions 9 October 2014 (1)

Action	Who?	Status
Send literature survey on ABUK (alpha-beta unsaturated ketones) to PC	MR	Done
Acquire LoA for CaAcAc sensitization endpoint	PMC	On hold until ABUK discussions finalised
Check if there are remaining registrations for 'Diammonium hexachlororuthenate'	PMC Sec	Done
Confirm if 'Diammonium hexachlororuthenate' is now Annex III exempt	PMC Sec	Done No remaining registrations
Existing irritation/ corrosion tests at CiToxLAB on 'Diammonium hexachlororuthenate': confirm with lab that the GLP reports can be amended to reflect the correct substance name	PMC/ RSA	Ongoing
Check if the physical chemical information and CoA/analytical data for the batch used in the existing irritation/corrosion tests are the same as for the second batch provided for RDT testing	PMC/RSA	Done
Amend ITS to reflect correct substance ID of 'Diammonium hexachlororuthenate'	WCA/ bibra	Done
Request test material for the outstanding tests on Tetraammonium decachloro-mu-oxodiruthenate	PMC Sec	Done
Dipotassium hexachloropalladate: request process definition	PMC	Done
Dipotassium hexachloropalladate: request official tonnage declaration	PMC	Done
Dipotassium hexachloropalladate: confirm whether or not the tonnage increase is handled under SCC	PMC Sec	Done
Ruthenium trichloride discuss speciation with Dave Boyd prior to conducting a data gap analysis	PMC Sec	Todo

Actions 9 October 2014 (2)

Action	Who?	Status
Update water solubility reported in ITS matrix for Dihydrogen hexahydroxyplatinate with new data	PMC/ WCA	Todo
Confirm tonnage band Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol	PMC/ WCA	Done
Dihydrogen hexahydroxyplatinate compound with 2-aminoethanol: conduct data gap analysis	bibra/ WCA	Done
Dihydrogen hexahydroxyplatinate compound with 2-aminoethanol: conduct acute daphnia test if confirmed by data gap analysis	PMC/ WCA	Ongoing
Request quote for peer review of DDP histopathology slides	PMC	Done
Ask for extended quote from Prof Foster to review histopathology slides of all PMC studies at CiToxLAB	PMC	Done
RDT tests: check study results for potential TSCA 8(e) implications	PMC	Ongoing
Initiate algae test on Diammonium sodium hexakis (nitrito-N) rhodate	PMC/ WCA	Done
Produce ITS addenda covering the implications of the new test results	WCA	Ongoing

Substance identification and sameness of PGMs

KLAUS ROTHENBACHER

KATRIEN ARIJS

ID cards

Ongoing:

- ID cards drafted for most PGMs in the testing programme
- ID cards for remaining PGMs will be circulated for input Q3/4 2015
- Existing ID cards will be recirculated for finalisation

2.2. Sameness: Update on diammonium hexachlororuthenate vs. 'Tetradoru'

Background

- 'Diammonium hexachlororuthenate' (CAS 18746-63-9, UVCB) is in fact 'Tetraammonium decachloro-mu-oxodiruthenate' (CAS 85392-65-0, mono-const. subst. = 'Tetradoru')
- Confirmed with individual registrants; updated inventory
- 'Diammonium hexachlororuthenate' not supported any longer

Since last meeting

- Reviewed and updated testing strategy
- Revising existing tests on AHCRu to reflect correct substance ID
- Initiated testing programme Ru compounds
- Requested test material

Inventory update – substance changes (1)

Tonnage band increases

- Rh(NO3)3: increase from 1-10t/y to 10-100t/y
- Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2): : increase from 1-10t/y to 10-100t/y
- Karstedt Concentrate? 10-100 tpa
- Diapotassium hexachloropalladate: increase from 10-100 tpa to 100-1000 tpa! – new; only confirmed yesterday; not considered in ITS yet
- Ruthenium trichloride: increase from 1-10t/y to 10-100t/y - new; only confirmed yesterday; not considered in ITS yet

Tetraammonium decachloro-mu-oxodiruthenate(4-) will replace AHCRu (same tonnage band = 10-100 tpa)

Inventory update – substance changes (2)

No more registrants for

- Dichlorotris(triphenylphosphine)ruthenium (CAS 15529-49-4)
- Diammoniumhexachloro ruthenate
- Iridium dioxide (CAS 12030-49-8Di-μ-chlorobis((1,2,5,6-eta)cycloocta-1,5-diene))diiridium (CAS 12112-67-3)
- Iridium dioxide (CAS 12030-49-8)
- Palladium dioxide (CAS 12036-04-3)

Cost implications: discussion tomorrow at PGM WG mtg.

Any Objections?

PGM testing programme

KLAUS ROTHENBACHER

Platinum Group Metals Ecotoxicity Testing

PMRC, Brussels, March 2015

3.1 Outstanding phys-chem tests

- Phys-chem test programme launched to fill remaining data gaps
- 26 substances in test programme
- Tests split between 3 laboratories – Fraunhofer, Siemens and BAM
- Samples requested before Christmas
- Fraunhofer (density and particle size)
  - » Two samples not yet received
  - » Density measurements complete for all received samples
  - » Particle size measurements ongoing. All received samples are powders and have had to be dispersed in organic solvents

3.1 Outstanding phys-chem tests

- Siemens (Vapour pressure and partition coefficient)
  - » All samples received and tested
  - » Draft reports received and under review
- BAM (Flammability and self-heating)
  - » All samples received and tested
  - » Draft report received and under review

3.1 Phys-chem tests: results summary

Testing House	Siemens			
Test Item	Results			
	Vapour pressure (p / hPa)			Partition coefficient (log Pow)
	20 °C	25 °C	50 °C	
14221-01-3 Tetrakis(triphenylphosphine)palladium	7.9×10^{-7}	1.3×10^{-6}	1.4×10^{-5}	
13965-03-2 Dichlorobis(triphenylphosphine)palladium	4.6×10^{-7}	8.2×10^{-7}	1.1×10^{-5}	
14024-61-4 Palladium di(4-oxopent-2-en-2-oate)	$< 4.6 \times 10^{-10}$	$< 8.9 \times 10^{-10}$	$< 1.8 \times 10^{-8}$	2.6
14874-82-9 Dicarbonyl(pentane-2,4-dinonato-O,O')rhodium	7.5×10^{-4}	1.3×10^{-3}	1.5×10^{-2}	
17185-29-4 Carbonylhydrotris(triphenylphosphine)rhodium	7.8×10^{-8}	1.4×10^{-7}	2.1×10^{-6}	
14694-95-2 Tris(triphenylphosphine) rhodium (I) chloride	$< 1.6 \times 10^{-8}$	$< 3.0 \times 10^{-8}$	$< 6.0 \times 10^{-7}$	
12092-47-6 Di-μ-chloro-bis(hapto-1,5-cyclooctadiene)dirhodium (I)	$< 2.2 \times 10^{-9}$	$< 4.2 \times 10^{-9}$	$< 8.4 \times 10^{-8}$	
25470-96-6 Carbonyl(pentane-2,4-dionato-O,O')rhodium	$< 9.8 \times 10^{-10}$	$< 1.9 \times 10^{-9}$	$< 3.8 \times 10^{-8}$	

3.1 Phys-chem tests: results summary

Testing House	BAM	
Test Item	Results	
	Readily combustable solids	Self-heating substances
13820-53-6 Disodium tetrachloropalladate	Not flammable solid	Not self-heating substance
16919-73-6 Dipotassium hexachloropalladate	Not flammable solid	Not self-heating substance
10025-99-7 Dipotassium tetrachloroplatinate	Not flammable solid	Not self-heating substance
10025-97-5 Iridium terachloride	Not flammable solid	
10025-83-9 Iridium trichloride (and hydrate)	Not flammable solid	

Ecotoxicity Testing Programme: Progress To Date

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)	-

Ecotoxicity Testing Programme: Progress To Date

Metal	Compound	Test	Progress	Result	Notes
Platinum	Dihydrogen hexahydroxyplatinate (HHPA)	Algae Inhibition of Growth (72 hours)	Test 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)	-

Ecotoxicity Testing Programme: Progress To Date

Metal	Compound	Test	Progress	Result	Notes
Platinum (cont.)	Dihydrogen hexahydroxyplatinate with 2-aminoethanol (HHPA-2AE)	*Daphnia* Immobility (48 hours)	-	-	**To be approved by WG.**
	Hexachloroplatinic Acid (HCPA)	ASRIT (3 hours)	-	-	**To be approved by WG.**

Ecotoxicity Testing Programme: Progress To Date

Metal	Compound	Test	Progress	Result	Notes
Ruthenium	Tetraammonium decachloro-mu-oxodiruthenate ((TERTADO Ru)	Algae Inhibition of Growth (72 hours)	May-June 2015 [Fraunhofer]	-	**Change of substance identity.** Awaiting test material (scheduled April 2015).
		Daphnia Immobility (48 hours)	May-June 2015 [Fraunhofer]	-	
		Fish Mortality (96 hours)	May-June 2015 [Fraunhofer]	-	
		ASRIT (3 hours)	May-June 2015 [Laus]	-	
Rhodium	Diammonium sodium hexakis (nitrito-N) rhodate (Rh Nitrite)	*Daphnia* Immobility (48 hours)	Completed July 2014 [Fraunhofer]	EC50 = 81.3 mg/L (11.8 as Rh)	-
		Algae Inhibition of Growth (72 hours)	Scheduled for March-April 2015 (Fraunhofer)	-	-
		ASRIT (3 hours)	-	-	**To be approved by WG.**
	Rhodium tri-nitrate	ASRIT (3 hours)	-	-	**To be approved by WG.**

Ecotoxicity Testing Programme: HHPA

- Daphnia acute EC50 for HHPA extrapolated above highest test concentration in definitive test
  - 30% effect at highest concentration

- At October 2014 meeting of PGM Working Group it was decided not to repeat this test because:
  - The reasons for varying exposure concentrations/ recoveries/ effects at similar nominal concentrations remains unclear
  - Any repeat test is very likely to suffer from similar issues
  - This data point is only required for HHPA (Pt PNEC driven by HCPA)
  - Owing to a tonnage increase, HHPA-2 aminoethanol will now require an acute *Daphnia* test and this can be used to support the HHPA acute *Daphnia* result

Ecotoxicity Testing Programme: 2015 Testing Proposals

- HHPA-2 aminoethanol
  - Change of tonnage (to be confirmed)
  - ***Daphnia* acute now required**
  - To be approved by WG
  - Following *Daphnia* result read across between HHPA and HHPA-2AE to be reviewed
  - Additional fish test with one / both substances may be required

- Hexachloroplatinic acid
  - Read across between HCPA and diammonium hexachloroplatinate considered appropriate

Test	diammonium hexachloroplatinate	hexchloroplatinic acid
Acute Daphnia	108 ug Pt/L (Fraunhofer 2014)	20.4 ug Pt/L (IBacon 2005)
		62 ug Pt/L (Safepharm 2001)

  - HCPA worst case
  - Propose to read across fish and algal results from HCPA
  - **ASRIT data gap for both substances – propose to test HCPA as worst case**
  - To be approved by WG

Ecotoxicity Testing Programme: 2015 Testing Proposals

- TERTADO Ru
  - Full base-set + ASRIT
  - Change of substance identity
  - Awaiting delivery of test substance
  - Tests scheduled for May-June (assuming test substance delivered in April)

- Diammonium sodium hexakis (nitrito-N)rhodate
  - Algal test + ASRIT
  - Algal test scheduled for March/April *(PMC note: approved at Oct. 2014 mtg)*
  - **ASRIT test required as data gap – need approval**
  - May be possible to read across between Diammonium sodium hexakis (nitrito-N)rhodate and rhodium trinitrate
  - Assess read across following algal result and conduct ASRIT with one or both substances

- Rhodium tri-nitrate
  - Change of tonnage band (1-10 to 10-100 tpa)
  - *Daphnia*, algal and fish tests available
  - **ASRIT now required as data gap – assess read across potential before testing**

PGM ecotox.: 2015 testing Recommendation PGM experts meeting

Substance	Test				Comment
Diammonium Sodium Hexakis (nitrito-N) Rhodate	acute algae		ASRIT		Algae agreed at Oct 2014 PGM expert mtg
HHPA - compound with 2-AE	acute algae	acute daphnia	ASRIT	act. fish	Agreed at Oct 2014 PGM expert mtg ASRIT approved at Oct. 2014 mtg.
CPA			ASRIT		Data gap, can read across to AHCPt then
Ru dimer	acute algae	acute daphnia	ASRIT	acute fish	Tests already agreed for AHCRu
Rh(NO3)3			ASRIT		Will assess potential for read across after algae test

Colour code	*already approved*	*recommend to approve*

- Additional cost: Algae (ca 7000 Euros) + ASRIT (4* 8000 Euros) + daphnia (5000 Euros) = 44 000 Euros
- Potential cost: HHPA acute fish= 10000 Euros
- Total cost up to 54 000Euros
- Remaining ecotox budget 2015: 117 000 Euros

Any Objections?

PGM genotixicity testing

- Updated ECHA guidance genotox testing: need TP for all Annex IX/ X tests, irrespective of tonnage
- No impact on our testing strategy

PGM Project
Tox Experts Group Meeting

Brussels

24 March 2105

Genotoxicity Studies
(Covance)

Substance and Test	Result	Status*
Tetraammonium decachloro-mu-oxodiruthenate		
Ames ï OECD 471		Awaiting TS
In vitro micronucleus test ï OECD 487		Awaiting TS
In vitro gene mutation ï OECD 476		Dependent on above
Dihydrogen tetrachloropalladate (2-) (CAS 16970-55-1)		
In vitro micronucleus ï OECD 487	Negative	Reporting
In vitro gene mutation ï OECD 476	Negative	Reporting
Tetraamminepalladium(II) diacetate (CAS 61495-96-3)		
In vitro gene mutation ï OECD 476		Ongoing
Palladium (II) di(4-oxopent-2-en-2-oate) (CAS 14024-61-4)		
Ames ï OECD 471	Negative	22-Oct-13
In vitro micronucleus test ï OECD 487	Negative	22-Oct-13
In vitro gene mutation ï OECD 476	Negative	9-Jun-14

* Report issue date

Genotoxicity Studies
(Covance)

Diammonium hexachloropalladate (CAS 19168-23-1)		
Ames ï OECD 471	Negative	7-Jan-14
In vitro micronucleus test ï OECD 487	Negative	6-Jan-14
In vitro gene mutation ï OECD 476	Negative	16-Apr-14
Dihydrogen hexahydroxyplatinate (CAS 51850-20-5)		
Ames ï OECD TG471	Mutagenic	3-Dec-13
In vitro micronucleus test ï OECD 487	Positive	22-Jan-14
Diammonium sodium hexakis(nitrito-N)rhodate (CAS 64164-17-6)		
Ames ï OECD TG471	Negative	25-Apr-14
In vitro micronucleus test ï OECD 487	Negative	15-Jul-14
In vitro gene mutation ï OECD 476	Negative	2-Oct-14
Palladium nitrate (CAS 10102-05-3)		
In vitro micronucleus test ï OECD 487	Negative	11-Jul-14
In vitro gene mutation ï OECD 476	Negative	18-Dec-14
Dirhodium trisulphate (CAS 10489-46-0)		
Ames ï OECD 471	Mutagenic	23-Feb-15

Rh(III) genotoxicity (1)

Background

- Positive findings for all substances, except Rh trinitrate (summary on next slide)
- Solid $Rh(NO_3)_3$ was tested
  - Sameness with solution (in HNO_3) confirmed
  - All studies considered valid

Agreed at last expert mtg

- Gel electrophoresis (CZE) work on hold until Ames data available
- Conduct Ames test with $Rh_2(SO_4)_3$ as referee substance
  - Solution in sulphuric acid was tested; no solid $Rh_2(SO_4)_3$ available

Ames test Rh2(SO4)3 positive

- No TSCA 8(e) filed since result in line with known effects of Rh(III)
- Need to discuss next steps: following slides

Rh(III) genotoxicity (2)

Existing studies Rh(III) genotoxicity (all considered valid)

Substance	Genotoxicity endpoint	pH value
CASRN 20765-98-4. Rhodium trichloride "hydrate"	Positive in vitro Ames test	<2
	Positive in vitro mouse lymphoma assay	
	Positive in vitro micronucleus assay	
	Positive in vivo micronucleus assay	
CASRN 10139-58-9. Rhodium trinitrate (solid)	Negative in vitro Ames test	1.3 (hydrate)
	Negative in vivo micronucleus assay	
CASRN 42204-14-8. Rhodium (III) acetate	Positive in vitro Ames test	Not known
CASRN 15492-38-3. Rhodium triiodide	Positive in vitro Ames test	4.2
Rhodium sulphate	**Positive in vitro Ames test**	

Rh(III) genotoxicity (3)

How to proceed – discussion

Should we read across positive findings to other Rh(III)?

- Referee compound tested positive
- Rh(III) likely toxic agent
- Recommended by Prof Kirkland
- Recommended by DECOS

Adobe Acrobat Document

Conduct CZE work? (ca 6 000 Euros)

Conduct MLA test on referee substance? (ca 16 000 Euros)

Microsoft Word Document

JM proposal?

JM comments (1)

- Need to remind ourselves that some conventional cut-offs are rules of thumb
  - Albeit ones that have regulatory implicationsé
- Very carefully reviewed each of the Rh(III) genotoxicity studies in the PMC dataset (accounting for protocol variations)
  - Partly for academic curiosityé .but also to again test weight-of-evidence for Rh nitrate as a negative
- Case can be made that for Rh(III), we are dealing with a continuum of biological (genotoxic) activity, based on:
  - Mainly Ames test outcomes (with other objective comparators)
  - Normalisation for equimolar concentrations, and tester strains of most relevance (mainly TA98 and TA102, plus also TA100)

JM comments (2)

- A pattern emerges:
  - There are more highly genotoxic Rh(III) compounds, including Rh trichloride and Rh triiodide
  - Less potent compounds typified by Rh acetate
  - Marginal/borderline positive in Ames: Rh sulphate. Latest study was worth doing as a datapoint
  - Rh nitrate where revertant increases never achieve statistical significance **nor** cross the conventional individual strain cut-off values.

- Accepted that the two Ames studies for Rh nitrate were both interpreted as negative:
  - But the protocols differed, e.g. only the latter one included the important TA102 strain, and only this study used the more sensitive pre-incubation method
  - Interestingly, as a secondary consideration, the in vivo MN study on Rh nitrate does have an activity blip at 44 hr, but a true dose-response was absent, and by 68 hr high-dose and control showed equivalent MN-RET frequencies

JM comments (3)

- Proposal:
  - Confirm another Rh nitrate standard formulation as a negative in Ames
  - Use the current conform approach including TA102 and pre-incubation
  - **End program if confirmed**
  - Why? ï because relevant to more than just REACH

PGM genotoxicity
Tonnage band increases

Rh(NO3)3 in 10 -100 tpa band now

- Cf. discussions previous slides
- No new genotox. tests required?

HHPA- compound with 2-AE in 10 – 100 tpa band now

- Data gap gene tox
- Read across from HHPA? = positive
- Testing proposal MN: test compound and read across to HHPA as worst case?

PGM genotoxicity testing – summary from PGM tox experts group

Status

- All scheduled tests completed or in reporting phase

Next steps

- Dihydrogen hexahydroxyplatinate: testing proposal for in vivo micronucleus study required? Or test compound and r/a to HHPA?
- Dihydrogen hexahydroxyplatinate compound with 2-aminoethanol: read across from HHPA = no new tests required
- Way forward Rh(III): update after PGM expert discussion

Sensitisation

Substance	Result	Status
Palladium (II) di(4-oxopent-2-en-2-oate)	Sensitiser based on RF studies	Complete 2-Apr-14
Diammonium hexachlororopalladate x 2	Sensitiser	Complete 3-Dec13 30-Jan-14
Diammonium sodium hexakis(nitrito-N)rhodate	Negative	Complete 6-Nov-13
Tetraammonium decachloro-mu-oxodiruthenate		Awaiting TS

Acute, Sub-acute and Reproduction Studies

Studies being conducted at two laboratories as follows:

- CiToxLAB – palladates and rhodate
  - Diamminedichloropalladium
  - Palladium (II) di(4-oxopent-2-en-2-oate)
  - Palladium dihydroxide
  - Diammonium hexachloropalladate
  - Tetraamminepalladium(2+) dichloride
  - Diammonium sodium hexakis(nitrito-N)rhodate
- LPT – platinates and rhuthenium:
  - Tetraammonium decachloro-mu-oxodiruthenate
  - Dihydrogen hexahydroxyplatinate
  - Diammonium hexachloroplatinate
  - Tetraammineplatinum dinitrate

Diamminedichloropalladium

- Main OECD 422 study completed at dose levels of 1500, 4500 and 12000 ppm (~ 100, 300 and 1000 mg/kg bw/day) in pelleted diet. Included additional females for toxicity assessment.
- Marked effects on body weight and food consumption at 12000 ppm with subsequent reduced mating performance. All high dose animals terminated on day 28 (no reproduction toxicity assessment). ñIt was not possible to clearly distinguish between the effects due to malnutrition and possible adverse effects of the test item é . at 12000 ppm.ò
- At 4500 ppm and below no general or reproductive toxicity.
- **NOAEL for systemic, reproductive and developmental toxicity was 4500 ppm (>300 mg/kg bw/day)**

Diammonium hexachloropalladate

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	Corn oil	100, 300, 600	100 suitable as high dose, 300 and 600 not tolerated	Reporting
Repeated dose oral toxicity ï OECD 407	Corn oil	10, 30, 100	NOAEL (systemic) 100 NOAEL (local) 30	Reporting
Combined repeat dose oral toxicity with repro/dev screen ï OECD 421	Corn oil	10, 30, 100	NOAEL (repro + dev) 100	Reporting

Tetraamminepalladium dichloride

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	pH adj water (pH 9)	100, 300	100 suitable as high dose, 300 not tolerated	14-Oct-14
Combined repeat dose oral toxicity with repro/dev screen ï OECD 421	pH adj water (pH 9)	4, 20,100	NOAEL (systemic) 4 (↓ bw gain M) NOAEL (repro + dev) 100	Reporting

Palladium (II) di(4-oxopent-2-en-2-oate)

Test	Vehicle	Dose levels	Result	Status
Acute oral toxicity - OECD 425	Distilled water	550, 2000	MLD 2000 mg/kg	Complete 17-Dec-13
Acute dermal toxicity - OECD 402	NA	2000	MLD > 2000 mg/kg	Complete 24-Apr-14

Diammonium sodium hexakis(nitrito-N)rhodate

Test	Vehicle	Dose levels	Result	Status
Acute oral toxicity - OECD 425	1% MC	175, 550, 2000	LD50 >2000 mg/kg	Complete 15-Jul-14
Preliminary repeat dose oral toxicity	1% MC	1000	1000 suitable as high dose	Reporting
Combined repeat dose oral toxicity with repro/dev screen ï OECD 422	1% MC	100, 300, 1000	NOAEL (systemic, repro + dev) 1000	Reporting

Palladium hydroxide

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	Corn oil	1000	1000 suitable high dose. No need for satellite females for toxicity	Complete 16-Jun-14
Combined repeat dose oral toxicity with repro/dev screen ï OECD 422	Corn oil	100, 300, 1000	NOAEL (systemic, repro + dev) 1000	Reporting

Dihydrogen hexahydroxyplatinate

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	Corn oil	1000	1000 suitable as high dose. No need for satellite females for toxicity.	Complete 22-Sep-14
Combined repeat dose oral toxicity with repro/dev screen ï OECD 422	Corn oil	100, 300, 1000	NOAEL (systemic, repro + dev) 1000	Reporting

Diammonium hexachloroplatinate

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	Corn oil	100, 300, 600	100 suitable as high dose, 125 and 200 not tolerated	Complete 24-Oct-14
Repeated dose oral toxicity ï OECD 407	Corn oil	10, 30, 100	NOAEL (systemic) 10 (kidney, stomach lesions, WBC changes*)	Reporting
Combined repeat dose oral toxicity with repro/dev screen ï OECD 421	Corn oil	10, 30, 100	NOAEL (systemic) 30 (mortality, macro kidney and stomach) NOAEL (repro) 30 (inc post-implantation loss and dec birth index) NOAEL (dev) 100	Reporting

- WBC: Lymphocytes increased in M +F at 100 (outside HCR) reflected in increased total white cell count
- Kidney: hyaline casts, tubular basophilia and lymphocytic infiltration
- Stomach: lympho-histio-granulocytic infiltration, lymphocytic or eosinophilic infiltration, and/or a chronic/subacute ulcerative inflammation

Tetraammineplatinum dinitrate

Test	Vehicle	Dose levels	Result	Status
Preliminary repeat dose oral toxicity	pH adjusted aq HNO_3	500, 750, 1000	1000 suitable as high dose	Complete 22-Aug-14
Combined repeat dose oral toxicity with repro/dev screen – OECD TG421	pH adjusted aq HNO_3	50, 250, 1000	NOAEL (systemic) 250 NOAEL (repro + dev) 1000	Complete 30-Jan-15

Tetraammonium decachloro-mu-oxodiruthenate

Test	Status
Acute oral toxicity (OECD 425)	Awaiting TS (Vehicle corn oil?)
Preliminary repeat dose oral toxicity	Awaiting TS (Vehicle corn oil?)
Repeated dose oral toxicity ï OECD TG407	Study design dependent on results of DRF
Repro/dev toxicity screen ï OECD 421	Study design dependent on results of DRF
Combined repeat dose oral toxicity with repro/dev screen ï OECD 422	Study design dependent on results of DRF

PGM acute/ RDT testing – Results summary

		NOAEL in mg/kg bw/d	
OECD	**422**	**407**	**421**
Diammonium Sodium Hexakis (nitrito-N) Rhodate	1000 (systemic, dev., reprotox)	-	-
Palladium dihydroxide	1000 (systemic) 1000 (reprotox)	-	-
Dipotassium Hexachloropalladate	-	30 (local effects) 100 (systemic)	100
Tetraamminepalladium(2+)dichloride	4 (systemic) 100 (reprotox)	-	-
Diamminedichloropalladium	> 300 (systemic, dev., reprotox)	-	-
AHCPt **Alert: classification change; STOT RE1!**	-	10	30 (general tox.) 30 (reprotox) 100 (pups)
HHPA	1000 (general tox.) 1000 (reprotox/ pups)	-	-
TPtNO3	-	-	250 (general tox.) 1000 (reprotox/ pups)

PGM acute/ RDT testing

Discussion

ITS changes due to tonnage band changes

Rhodium trinitrate

10 – 100 tpa

Skin irritation
Classify on basis of extreme pH - although acid-reserve indicates not corrosive. Company specific data (on hydrate – solid; solution) available - Corrositex indicates Cat 1B – Confidential?
TEST OECD TG 431 - in vitro test for corrosivity?

Eye irritation
Waive on basis of extreme pH/irritating to skin

Skin sensitization
Data available – Skin sens 1

In vitro gene mutation study in bacteria
Data available – Ames negative

Acute toxicity, oral route
Data available – Acute tox 4

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Rhodium trinitrate

Continued…

In vitro cytogenicity in mammalian cell
In vivo data available – negative

In vitro gene mutation study in mammalian cells
TEST In vitro L5178Y Mouse lymphoma cells Gene mutation assay at hprt locus?

Acute toxicity, inhalation, dermal
Waive on basis of skin corrosive

Short-term repeated dose toxicity and Reproductive/Developmental toxicity screen
Read-across from OECD 422 on Diammonium sodium hexakis(nitrito-N)rhodate 64164-17-6

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Tetraammonium decachloro-mu-oxodiruthenate(4-)

10 – 100 tpa

Skin irritation
Data available - not irritant
[studies done on "Diammonium hexachlororuthenate" - confirm valid]

Eye irritation
Data available (in vitro & in vivo) – irreversible effects in vivo
[studies done on "Diammonium hexachlororuthenate" - confirm valid]

Skin sensitization
TEST OECD 429 LLNA

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Tetraammonium decachloro-mu-oxodiruthenate(4-)

Continued…

In vitro gene mutation study in bacteria
Screening test and Ames test OECD 471

Acute toxicity, oral route
TEST OECD 425

In vitro cytogenicity in mammalian cells
TEST OECD 487 in human lymphocytes

In vitro gene mutation study in mammalian cells
TEST OECD 476 if Ames and MN tests –ve

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Tetraammonium decachloro-mu-oxodiruthenate(4-)

Continued…

Acute toxicity, inhalation
Not relevant – enabling studies
[studies done on "Diammonium hexachlororuthenate" - confirm valid]

Acute toxicity, dermal
Assess need for 2nd route, dermal after acute oral test completed

Short-term repeated dose toxicity
TEST OECD 407 or combined OECD 422 to be decided on completion of acute oral study

Reproductive/Developmental toxicity screen
TEST OECD 421 or combined OECD 422 to be decided on completion of acute oral study

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Dihydrogenhexahydroxyplatinate, compound with 2-aminoethanol (1:2)

10 – 100 tpa

Skin irritation
TEST OECD 431 and 439 (EpiSkin)

Eye irritation
TEST OECD 437 (BCOP)
In vivo TEST dependent on result of in vitro tests (eye, skin)

Skin sensitization
Data gap Potential WoE based on HHPA & aminoethanol (REACH registration) - not significant sensitizer

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Dihydrogenhexahydroxyplatinate, compound with 2-aminoethanol (1:2)

Continued…

In vitro gene mutation study in bacteria
Data available – positive

Acute toxicity, oral route
Data available - LD50 > 2000 mg/kg bw

In vitro gene mutation study in bacteria
Data available – positive

Acute toxicity, oral route
Data available - LD50 > 2000 mg/kg bw

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Dihydrogenhexahydroxyplatinate, compound with 2-aminoethanol (1:2)

Continued…

Acute toxicity, inhalation
Waive as only handled as a solution

Acute toxicity, dermal
Waive on basis of low oral toxicity

Short-term repeated dose toxicity/Repro-Dev toxicity screen
Data gap WoE approach based on data from Dihydrogen hexahydroxyplatinate and 2-aminoethanol

In vivo genotoxicity
[Test proposal for Dihydrogen hexahydroxyplatinate]

Discussion: Testing requirements last-minute changes

- Dipotassium hexachloropalladate: increase from 10-100 tpa to 100-1000 tpa! – new; only confirmed yesterday; not considered in ITS yet
  - Ecotox: testing proposals
    - Bioaccumulation
    - Long-term aq. tox (fish)
    - Soil tox?
  - Mamm. tox: testing proposals
    - 90d RDT – need TK study?
    - Prenat. dev. tox
    - 2-Gen repro?
- Ruthenium trichloride: increase from 1-10t/y to 10-100t/y - new; only confirmed yesterday; not considered in ITS yet
  - Ecotox:
    - ASRIT
  - Mamm. tox
    - Genotoxicity tests (Ames, MLA, hprt)

PGM acute/ RDT testing – summary from PGM tox experts group

Status

- All scheduled tests completed or in reporting phase

Rh(NO3)3 in 10 -100 tpa band now

- RDT - Read-across from Diammonium sodium hexakis(nitrito-N)rhodate not possible, need OECD 422 study (120 000 Euros)

HHPA- compound with 2-AE in 10 – 100 tpa band now

- Data gaps
  - Skin/ eye irritation
  - Sensitisation – read across from HHPA and 2-AE?
  - RDT - read across from HHPA and 2-AE?

Dipotassium hexachloropalladate

Ruthenium trichloride

Current status of PNEC and DNEL refinement

KLAUS ROTHENBACHER

4.1 Status of PNEC derivation: Pd

- PNECs expressed as concentration of Pd, single PNEC to cover all Pd substances
  - » Based on ecotoxicity data for DDP as worst case

PNEC	Value	Justification
Freshwater	0.027 µg Pd/L	Algal NOEC, AF 50
Marine water	0.0027 µg Pd/L	Algal NOEC, AF 500
STP	1.46 mg Pd/L	EC10 from ASRIT, AF 10
FW sediment	0.274 mg /kg Pd dw	NOEC from 28-d chironomid study, AF 100
MW sediment	0.027 mg /kg Pd dw	NOEC from 28-d chironomid study, AF 1000
Terrestrial	0.027 mg kg Pd dw	EQP

Status of PNEC derivation: Other metals

- Platinum
  - » Preliminary PNECs derived based on available data
  - » Some ecotox testing ongoing, PNECs to be finalised once results received
- Rhodium and ruthenium
  - » Testing ongoing, PNECs to be derived once results received
- Iridium
  - » No PNECs required

PNEC derivation – summary from PGM tox expert group mtg

Status

- Palladium
  - PNECs finalised
- Platinum
  - Preliminary PNECs derived based on available data
  - Some ecotox testing ongoing, PNECs to be finalised once results received
- Rhodium and ruthenium
  - Testing ongoing, PNECs to be derived once results received
- Iridium
  - No PNECs required

Next steps

- Complete scheduled testing in 2015 (if approved)
- Derive Pt PNECs in Q2
- 2015, derive other PNECs once data is available

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

DNELs needed for each health effect and each relevant exposure pattern

Two main types:

$DNEL_{long\text{-}term}$

$DNEL_{acute}$

Systemic and local effects

Reproductive toxicity (fertility impairment and developmental toxicity)

However, lack of dose-descriptors generally precludes DNEL derivation for acute toxicity, irritation/corrosion, sensitization

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Exposure pattern	DNEL/DMEL (appropriate unit)	
	Workers	General population [3]
Acute – inhalation, systemic effects[1]	worker-DNEL acute for inhalation route-systemic	General population-DNEL acute for inhalation route-systemic
Acute – dermal, local effects[2]	worker-DNEL acute for dermal route-local	General population-DNEL acute for dermal route-local
Acute – inhalation, local effects[2]	worker-DNEL acute for inhalation route-local	General population-DNEL acute for inhalation route-local
Long-term – dermal, systemic effects[1]	worker-DNEL long-term for dermal route-systemic	General population-DNEL long-term for dermal route-systemic
Long-term – inhalation, systemic effects[1]	worker-DNEL long-term for inhalation route-systemic	General population-DNEL long-term for inhalation route-systemic
Long-term – oral, systemic effects[1]	Not relevant	General population-DNEL long-term for oral route-systemic
Long-term – dermal, local effects[2]	worker-DNEL long-term for dermal route-local	General population-DNEL long-term for dermal route-local
Long-term – inhalation, local effects[2]	worker-DNEL long-term for inhalation route-local	General population-DNEL long-term for inhalation route-local

1. Units for systemic exposure are mg/m3 for inhalation, and mg/kg bw for oral and dermal exposure

2. Units for local effects are mg/m3 for inhalation; and for dermal exposure: mg/cm2 skin, mg/person/day (e.g., calculated based on the deposited amount per cm2 times the actually exposed body area), or a measure of concentration (% or ppm)

3. General population includes consumers and humans via the environment. In rare cases it may also be relevant to derive a DNEL for specific subpolulations, such as children.

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24 PGM substances >10 tpa

Repeated dose and Reproductive/Developmental toxicity data currently available:

Å Diammonium Sodium Hexakis (nitrito-N) Rhodate (draft)	OECD 422
Å Palladium dihydroxide (draft)	OECD 422
Å Diammonium hexachloropalladate (draft)	OECD 407 & OECD 421
Å Tetraamminepalladium(2+)dichloride (draft)	OECD 421
Å Diammoniumdichloropalladium (draft)	OECD 422
Å Ammonium hexachloroplatinate (draft)	OECD 407 & OECD 421
Å Dihydrogen hexahydroxyplatinate (draft)	OECD 422
Å Tetraammine platinum nitrate (final)	OECD 421
Å	
Å Tetraamminepalladium(2+) hydrogencarbonate	OECD 407

Aim to start deriving DNELs – long-term, systemic in April 2015.
Estimate 2-3 days/set. About two substances/month

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DNEL derivation – summary from PGM tox expert group mtg

Status

- On schedule, except for Ru-compound
- Confirm after expert meeting that no additional studies are required

Next steps

- Derive DNELs once above hazard assessment completed
- Planned for 2015-2016

CLP update – CLP notifications

Previous meeting

- Discussed classification changes
- Recommended to lead notifiers to update classifications accordingly

ITS Matrices

- Were updated in March 2015 with all new test results
- Classifications also updated in line with new data

Next Steps

- Recommend to update classifications only once all data are ready
- Exception: classifications that require action 'without undue delay'

Any Objections?

A.O.B.
Next meeting
Closing remarks

Thank you!