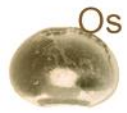
Precious Metals and Rhenium Consortium PGM Experts meeting

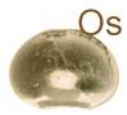
Brussels

9th October 2012



1. Introduction and welcome

- Competition Law reminder
- Approval of the Agenda
- Approval of minutes last meeting



2. PGM Testing Programme

2.1 Enabling- /phys.-chem. Tests

Oxidising Properties – tests at BAM

- Testing completed
  - BAM, Berlin
  - Results presented at previous meetings
  - Follow-up test: confirm ox. prop. of dihydrogen hexahydroxyplatinate
    - Was: Cat. 1 based on read across
    - Now: not an oxidiser, no classification necessary

Water Solubility

- Used 3 different test methods
  - OECD 105 (shake flask test) - JMTC
  - Modified shake flask test - JMTC
  - TD testing – CANMET

- Tests completed, final reports received and circulated
- Karstedt concentrate on hold until sameness discussions with Reconsile consortium finalised

Bio-elution tests

- Status
  - Testing completed; at CIMM, Chile
  - PdO: no sample provider found in time for tests
  - Draft reports received
  - PSD data still outstanding
- Draft results: next slides

Bio-elution tests - Discussion

- Bio-elution of fine powders may be overestimated
  - Test principle
    - Powders are shaken in elution medium
    - Solutions are filtered through 0.22 um filter (= 220 nm)
  - Particles < 0.2 um may pass filter and may be reported as 'dissolved'
- Options
  - Accept data as worst-case values if they do not result in risk findings
  - Ultracentrifugation will likely remove fine particles
    - Repeat test and ultracentrifuge samples
    - Or: repeat test with critical samples only

Bio-elution tests - Results

BIO-ELUTION PRELIMINARY RESULTS, expressed as % solubility of metal (ion) content

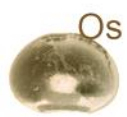
From CIMM report

Fluid type	Exposure time	Platinum powder	Palladium powder	Palladium dihydroxide	Palladium(II)di (4-oxopent-2-en-2-oate)	Rhodium powder	Diammonium sodium hexakis(nitrito-N)rhodate	Ruthenium powder	Platinum Black	Palladium black	Rhodium black	Ruthenium black
Gastric fluid	2h	2×10^{-4}	0,32	77,8	22,6	7×10^{-4}	115	5×10^{-5}	0,05	18,3	0,024	0,011
Perspiration fluid	168h (1 week)	1×10^{-4}	0,003	2,6	1,9	7×10^{-5}	38,4	9×10^{-6}	0,15	0,22	0,021	0,005
lysomomal fluid	24h	X	X	X	X	X	X	X	0,01	0,5	0,03	0,02
	168h (1 week)	X	X	X	X	X	X	X	0,08	52,9	0,04	0,05
Interstitial fluid	24h	X	X	X	X	X	X	X	7×10^{-4}	4×10^{-4}	0,03	0,005
	168h (1 week)	X	X	X	X	X	X	X	1.8×10^{-3}	6×10^{-4}	0,03	0,006

Surface area, PSD & deposition

N-BET (m^2/g)		0,08	0,23	133	2,63	0,181	1,09	0,44	>=25* (31)	25,5	3,61	23,6
PSD (µm) Fraunhofer (d_{50})		286	52	0,67	2,1	179	9,3	8.18* (6.1)	0,41	0,39	21	2,3
PSD Aero (µm) DMT		31,39	30,2	29,8	38,2	26,9	29	20,1	7,4	24,1	28,1	21,7
Dustiness (%) DMT		72,65	284,26	138,92	232,05	262,66	237,16	48,48	205,45	457,02	514,78	401,12
Resp. tract deposition (%)	TB	0,098					0,2					
	Pulmonary	0,053					0,32					

*value from CIMM report - origin of data not clear. Value in parentheses from Fraunhofer report

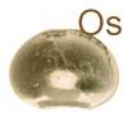


Dustiness tests/ MPPD modeling

- Tests completed, final reports issued
- Results presented at previous meeting

Irritation/corrosion testing

- Testing strategy
  - In-vitro skin irritation (OECD 439) – if positive: OECD 431
  - In-vitro skin corrosion (OECD 431) – if positive: stop
  - In-vitro eye irritation (ICE or BCOP) – if positive: stop
  - In-vivo eye irritation
- Skin corrosion data needed to decide on other tests
  - Eye irritation
  - Sensitisation
  - Acute toxicity
  - (Genotoxicity)



Irritation/corrosion testing

- All substances finalised, except Tetraammineplatinum dinitrate
- Potential TSCA 8(e) reporting requirements

Substance	In vitro skin (EPISKIN) test	In vitro eye (e.g. BCOP or ICE) test	In vivo eye irritation test	
Diammonium hexachlororuthenate (CAS 18746-63-9)	Not irr./corr.	ICE neg	**Cat. 1**	Initial in-vivo data indicate possible irritation, need to confirm with water solubility data (in progress)
Carbonyl(pentane-2,4-dionato-O,O')(triphenylphosphine)rhodium (CAS 25470-96-6)		-	-	Due to reduction in tonnage, substance now qualifies for Annex III exemption. No testing required any longer.
Diammonium sodium hexakis(nitrito-N)rhodate (CAS 64164-17-6)	Not irr./corr.	ICE neg.	neg.	ICE
Diamminedichloropalladium (CAS 13782-33-7)	Not irr./corr.	ICE neg.	**Cat. 1**	ICE
Palladium (II) di(4-oxopent-2-en-2-oate) (CAS 14024-61-4)	Not irr./corr.	ICE neg.	**Cat. 1**	N/A
Platinum dichloride (CAS 10025-65-7)				Out of scope now
Tetraammineplatinum dinitrate (CAS 20634-12-2)	Not irr./corr.	BCOP neg.	ongoing	Supplied as solution, max. conc. 6.6%. Makeup of 20% solution from solid is not possible since solid is not isolated (explosivity)
Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes / Karstedt concentrate (CAS 68478-92-2)	(X)	(X)	(X)	Data sharing under discussion with Silicones sector. Suggest to put testing on hold. (Will decompose in aqueous solution. Consider waiver possibility. Predicted to be a marked irritant.)
Dihydrogen hexahydroxyplatinate (CAS 51850-20-5)	Not irr./corr.			

Enabling tests - AOB

- Summary report enabling tests
  - In preparation by WCA
- Relative density/ granulometry
  - Data gap for most substances
  - Can members determine this in-house?

PGM testing programme - AOB

- New sample requests
  - Estimate: ca 1000g needed
  - Samples to be stored at CRO (CRL or CiToxLAB)
  - Risk management: if possible,
    - Sample provider to ship only 200g (sufficient for all tests except RDT)
    - Sample provider to store remaining 800g at own safe storage facility
    - Invoice full amount to PMC
- TSCA 8(e) reporting requirements
- Refining of unused samples

2.2 Fast-track testing: Diamminedichloropalladium

DIAMMINEDICHLOROPALLADIUM: ECOTOXICOLOGY STUDIES

Study	CRO	Status	Comments
ALGAE (OECD 201)	Fraunhofer	Completed	Exposure concentrations (based on Pd analysis) were at 26-62% of nominal at the start of the test and dropped to 14-21% of nominal after 72 hours. Toxicity results are therefore based on geometric mean measured exposure concentrations. Based on the geometric mean measured Pd concentrations; EC50 Yield = 2.03 mg/L Pd/ 4.03 mg/L DDP EC50 Growth Rate = 2.96 mg/L Pd/ 5.88 mg/L DDP NOEC Growth Rate & Yield = 1.33 mg/L Pd/ 2.64 mg/L DDP
DAPHNIA (OECD 202)	Fraunhofer	Completed	Initial definitive test completed without filtration of analytical samples. Test requires repeat (no extra cost). Results of repeat definitive test indicate an **EC50 of 69.91 ug/L DDP** and a NOEC of 40.77 ug/L DDP.
FISH (OECD 203)	Fraunhofer	Completed	Results from definitive fish test indicate an EC50 of 306 ug/L DDP and a NOEC of 93.2 ug/L DDP. Very slight contamination of control solutions (likely caused in transfer of fish) does not appear to invalidate the study (factor of >100 less than NOEC).

DIAMMINEDICHLOROPALLADIUM: TOXICOLOGY STUDIES

Study	CRO	Status	Comments
Episkin OECD TG431	LAB		Not required as OECD 439 indicates not irritating. Study cancelled 2 Mar 12.
Episkin OECD TG439	LAB	Issued	Non irritant
in vitro eye irritation (ICE)	LAB	Issued	Non irritant
in vivo eye irritation OECD TG405	LAB	Issued	3 animals , 21 days observation. Irreversible effects.
Sensitisation OECD TG429 (LLNA)	HARLAN	Issued	NON-SENSITISER using 25% in 7 : 3 ethanol : distilled water
Ames screen	COVANCE	Issued	Negative
GLP Ames	COVANCE	Issued	Negative
in vitro micronucleus assay in human lympocytes	COVANCE	Issued	Negative
hrpt assay - mouse lymphoma cells	COVANCE	Main study ongoing	Range finder results - no tox at up to 40ug/ml. Doses for Expt 1 3 hour -/+ S-9: 5, 10, 20, 25, 30, 35 and 40 ug/mL. Expt 1 negative (23/8/12). Expt 2 ongoing.

DIAMMINEDICHLOROPALLADIUM: TOXICOLOGY STUDIES

Study	CRO	Status	Comments
Acute oral toxicity - acute toxic class OECD TG423	CHARLES RIVER UK	Issued	Category 4 (LD50 >300 to 2000 mg/kg)
Preliminary to combined oral repeat dose toxicity with reproduction/development toxicity screening test	CHARLES RIVER UK	MM review complete. Revised report with sponsor for comment 13-Aug-2012	Issue of report to be held pending outcome of new study
Combined oral repeat dose toxicity with reproduction/development toxicity screening test OECD TG422	CHARLES RIVER UK	Study terminated 11-July-12	422 study design not adopted due to toxicity - repeat dose study only. New study and preliminary to be conducted at CiTox LAB. October draft report requested. Report issue may be held pending new study.
Development of methodologies for the formulation analysis of palladium in oral gavage formulations	CHARLES RIVER UK	Completed 10-Feb-12	Acceptable formulation in 0.5% HPMC with good analytical accuracy.
Validation of methodologies for the formulation and analysis of palladium in oral gavage dosing formulations	CHARLES RIVER UK	Issued 27/9/12	
Acute dermal toxicity - OECD TG402	CiToxLAB	Draft report sent to Sponsor 27/9/12	MLD > 2000 mg/kg

DDP Repeated toxicity testing (RDT)

- OECD 422 study at Charles River terminated
- Need to repeat study + extensive range finder
- New CRO: CiToxLAB
- Range finder to start in October 2012

- But: Study will not be completed in time for 2013 registration!
- We need a Plan B for DNEL derivation

DDP DNEL

- Data from OECD 422 will not be available for 2013 registration
  - No valid RDT study available on DDP(data gap)
  - Need to develop tentative DNEL
  - One available/ valid RDT study on Pd compounds:
    - Tetraamminepalladium hydrogencarbonate (out of scope substance)
    - Wragg et al. (1997) 28-day repeated dose oral (gavage) toxicity – rat
    - 1.5, 15, 150 mg/kg bw/day (OECD TG407)
    - NOEL 1.5 mg/kg bw/day; NOAEL 15 mg/kg bw/day
- Suggest to derive tentative DNEL based on Wragg et al. study
- Any objections?

DDP PNEC

- All scheduled ecotox tests successfully completed
- Only acute tests = high assessment factors (AF) = low PNECs
- Possibility to refine if necessary – depending on ES needs

Diamminedichloropalladium (DDP) (CAS 14323-43-4) F

Endpoint	EC50	AF	PNEC	Unit
$PNEC_{freshwater}$	69.91	1000	0.07	µg/L DDP
$PNEC_{marinewater}$	69.91	10000	0.007	µg/L DDP
$PNEC_{water,\ intermittent}$	69.91	100	0.7	µg/L DDP
$PNEC_{microorganisms}$	EC10: 29000	10	2900	µg/L DDP
$PNEC_{sediment,\ FW}$	equilibirum partitioning based on PNECwater		0.054	µg/kg DDP
$PNEC_{sediment,\ SW}$			0.991	µg/kg DDP
$PNEC_{soil}$			0.036	µg/kg DDP
$PNEC_{oral}$	not required			

2.3 PGM testing programme

Sensitisation

- Scope finalised
  - Palladium di(4-oxopent-2-en-2-oate) a.k.a. Pd(ac)2
  - Diammonium hexachloropalladate
  - Diammonium sodium hexakis(nitrito-N)rhodate
  - Diammonium hexachlororuthenate
  - *Testing completed: DDP: not a sensitizer*
  - *On hold : CAS 68478-92-2 Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes / Karstedt concentrate*
  - *No testing proposed: Dihydrogen hexahydroxyplatinate (new proprietary data available)*
- Testing started at CiToxLAB
  - Scope: LLNA, 5 animals, individual lymph nodes reported, concurrent pos. control = studies can also be used for other jurisdictions, e.g., in US

Genotoxicity

- Majority of testing scope agreed (s. next slides)
- 'Genotoxicity Task Force' set up to advise on open issues
  - Rh(III) genotoxicity
  - Read across/ reference substances for future testing (Platinum- and Rhodium- nitrate)
    - E.g. $Rh(NO_3)_3$: existing tests on solid substance, but only declared as solution in HNO_3
- Information requests: PMC ID card exercise (+ core set of spectra) to support discussions
- Expert face-to-face meeting on sameness discussions planned for mid-November

Genotoxicity

- Updated testing strategy based on input David Kirkland
- Suggest to start testing of already agreed scope
- Agreed CRO: Covance

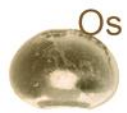
Substance	In vitro gene mutation test in bacterial cells - screening test	In vitro gene mutation test in bacterial cells (Ames test - OECD TG471)	In vitro micronucleus test in mammalian cells (OECD TG487)	In vitro mammalian cell mutation assay (OECD TG476)
CASRN 18746-63-9. Diammonium hexachlororuthenate	X	X	X	Required if Ames & MN tests negative
CASRN 16970-55-1. Dihydrogen tetrachloropalladate(2-)		Reliable data available	X	Required if MN test negative
CASRN 10102-05-3. Palladium dinitrate		Reliable data available	X	Required if MN test negative
CASRN 13782-33-7 Diamminedichloropalladium	X	X	X	Required if Ames & MN tests negative
CASRN 61495-96-Tetraamminepalladium(II) diacetate	(X)[1]	(X)[1]	Waive (read across in vivo result from tetraammine palladium(II) hydrogen carbonate	X[1]
CASRN 14024-61-4. Palladium (II) di(4-oxopent-2-en-2-oate)	X	X	X	Required if Ames & MN tests negative
CASRN 19168-23-1. Diammonium hexachloropalladate	X[2]	X[2]	X	Required if Ames & MN tests negative
CASRN 51850-20-5. Dihydrogen hexahydroxyplatinate	X	X	X	Required if Ames & MN tests negative
CASRN 18496-40-7. Platinum dinitrate			requirement to be discussed (see Section 4.2)	
CASRN 68478-92-2. Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes / Karstedt concentrate[3]			X	Required if MN test negative
CASRN 64164-17-Diammonium sodium hexakis(nitrito-N)rhodate	X	X	X	Required if Ames & MN tests negative

Genotoxicity (ctd.)

Substance	In vivo gene mutation assay	In vivo reticulocyte micronucleus assay (OECD TG474)
CASRN 16941-12-1. Hexachloroplatinic acid (or salt of)		X
CASRN 18496-40-7. Platinum dinitrate	On hold	On hold

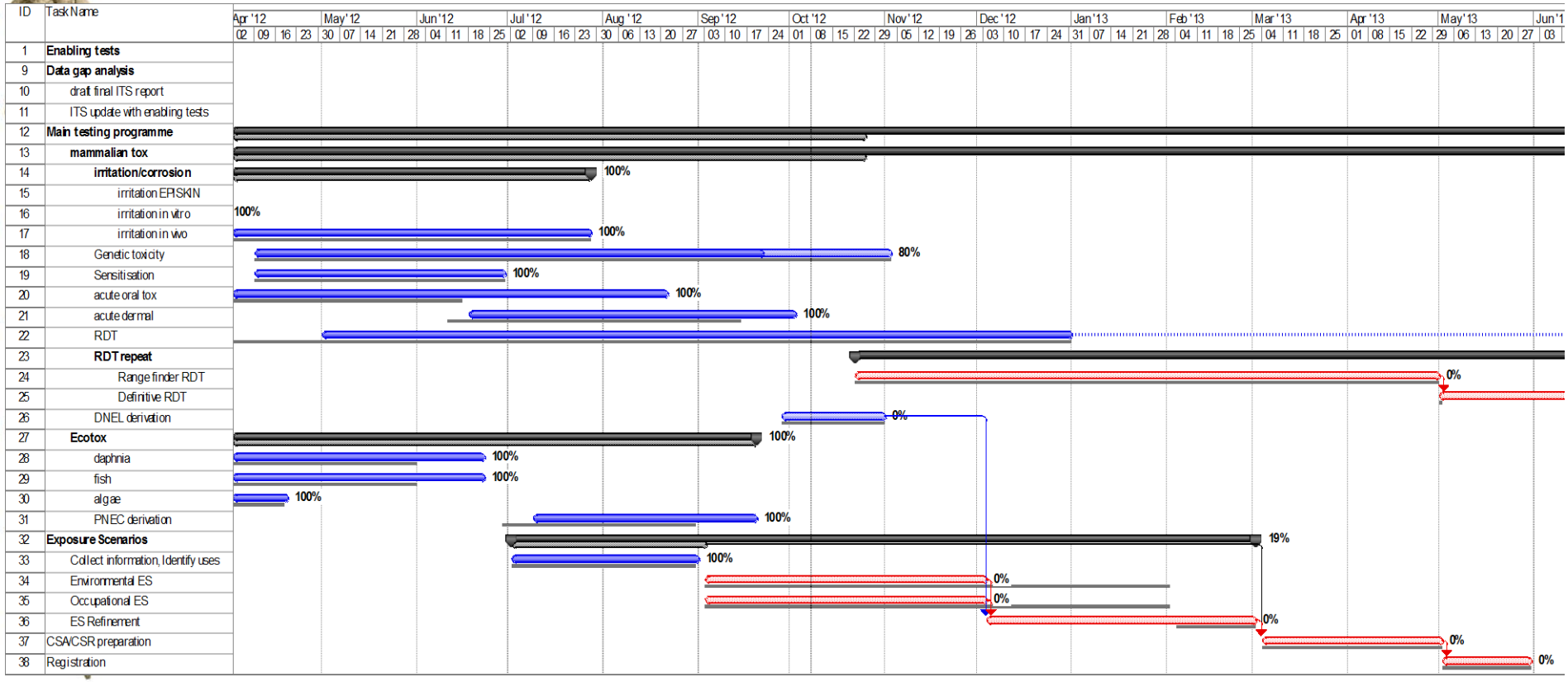
Ecotox testing

- Scope finalised
- Testing to start in Q3 2012
- Agreed CROs: Brixham (UK) and Fraunhofer (Schmallenberg, D)



3. Project Planning - Timeline

Timeline fast-track - for 2013 deadline



Timeline full testing programme