Precious Metals Consortium

PGM Tox Experts Meeting – Minutes

Brussels, 19 April 2016 (1-5:30 pm)

Actions	Who?	When?	Status
Circulate Sameness meeting minutes to Mark Raffray and Dave Boyd	KR		**Done**
Check if the reported EC50 value for HHPA is correct referring to solubility of that compound	WCA	<June 2016	
Check timeslot for 2nd LLNA test KC	JM	<June 2016	
Inform TE on vehicle & dosing for RDT test with TetradoRu	JM	When draft protocol is available	
Update ITS and IUCLID as appropriate, w.r.t. the Rh(III) genotox classification decisions.	Bibra	15 September	
Include additional wording in the Pd tetraammines AMES study record	Bibra	30 June 2016	
Revise qualitative hazard bandings for Pd dossiers	Bibra	<June 2016	
Check the complete Pt genotox database	Bibra	<15 June 2016	
Provide to EBRC a brief explanation what hazard is driving the Pt DNELs	JM/Bibra	<June 2016	Done
Share the relevant CSR sections as an example for a qualitative apporach for occup. exposure/risk assessment with PMC Tox Experts	BASF	Week of 25 April 2016	Done
Check availability of Steven V and inform with sub-group members for most suitable date	JM	Week of 25 April 2016	Done

1. Welcome and Introduction

1. Confidentiality and Competition Law

Participants were reminded on their obligation to comply with Confidentiality and Competition Law.

2. Tour de table and apologies

The list of participants is available in Annex 1.

3. Approval of the agenda

No remark were made. The agenda was approved.

2. PGM testing programme / Summary PGM tox experts mtg

1. PGM Phys-chem testing

For Palladium dinitrate, Tetraamminepalladium(2+) dihydroxide [***post meeting note**: this substance does not need testing as it can not be isolated as a solid*], Tetramminepalladium(2+) diacetate, Platinum dinitrate, Rhodium tris(2-ethylhexanoate) and Palladium sulphate, it was decided that solids need to be registered next to solutions (cfr. PGM Sameness meeting June 2015). Both forms will be covered by the same REACH Registration dossier. Three testing labs were contacted, and testing will not affect the internal PGM registration deadlines.

The PGM Tox Experts did not oppose to test with BAM.

ACTION:

- **KR to circulate minutes Sameness meeting to Mark Raffray and Dave Boyd**

2. PGM ecotox testing

HHPA-2AE and Karstedt concentrate

Ecotox testing for HHPA-2AE is running as foreseen (finalisation in July 2016), and the ecotox testing program for Karstedt concentrate (‚KC') has just been approved.

ACTION:

- **WCA to check if the reported EC50 value for HHPA is correct as the water solubility of that compound is similar.**

A hydrolysis pre-test for KC showed that the concentration of Pt and the ligand reduced over time.

The TE recommends to conduct an assessment of the technical feasibility of this mandatory test before deciding on a full hydrolysis test on Karstedt.

RuCl3

The Range-finder test for RuCl3 showed rapid disappearance of the test substance from the medium, with low Ru concentrations in solution remaining. RuCl3 can be considered a ‚difficult to test substance' in aquatic media because of its changing speciation.

The TE recommends to check the available literature on dissolution kinetics before deciding on the way forward.

Following the outcome of the Pd ecotox testing program, WCA proposed to change Chronic M factors for diamminedichloropalladium, palladium dichloride an disodium tetrachloropalladate from 100 to 10. **The TE group agrees with this proposal**

3. PGM HH testing

Karstedt concentrate:

The HH testing for KC is running as scheduled. The KC formulation is shown to be stable. As KC is designed to interact with organics, the stability in corn oil (proposed vehicle) needs to be checked before continuing testing.

The TE group recommends to check the stability of KC in corn oil (as determined by IR spectra) before initiating the acute and repeated dose testing.

For KC HH testing, high levels of chloride should be avoided (cfr. false positives), and the Cl- concentration should be specifically mentioned in the CoA [*post meeting note: the Cl content of the KC test sample <0.0575%*]. The Lead Registrant confirmed the testing sample is a representative one.

For the OECD442B test, vehicle selection is critical; acetone/olive oil is considered a suitable option, whereas DMSO is not [*post meeting note: vehicle selection is a key step in the OECD442B protocol as provided to PMC*].

ACTION:

- **JM – check time slot when OECD442B test can be repeated (evt adapted protocol) if required.**

HHPA-2AE

The HHPA-2AE testing showed the substance needs a classification as Skin Corrosive Cat 1B/C and, consequently, also a classification (not labelling) as serious eye damage.

The TE agrees with this classification; local tissue reactivity can be expected when exposed.

It is repeated that an in vivo micronucleus test is included as a testing proposal in the registration dossier.

The repeated-dose testing is currently running.

RuCl3

The RuCl3 testing is running as scheduled. Substance stability in diet at 10000 ppm has been confirmed. No additional discussion.

TetradoRu

A 14-d DRF study for Repeated Dose Toxicity with TetradoRu indicates some minor effects on male and female test animals. The effects were not considered sufficient to do a split testing (OECD407&421); a 20% effect level is considered critical, but the effect level after 14d testing are max 14.5% for male and max 6.3% for female animals.

The TE recommends to go ahead with a combined study (OECD422).

ACTION:

- **JM to inform the TE group the vehicle and dosing for the final test before initializing.**

The TE agrees with the updated HH Hazard classifications for the Pd group substances:

°Pd(OH)2 : not classified → 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,

°(NH4)2PdCl6: Additional classification as Acute tox 4 (dermal)

°K2PdCl6: Additional classification as Acute tox 4 (dermal)

Rh(III) genotoxicity

For the Rh(III) genotoxicity, it was agreed by the PGM WG in Feb 2016 to classify RhCl3 as Muta2 based on the available testing data. In the same conf call, it was also agreed to read-across this Muta2 classification '*to the relevant soluble Rh(III) compound in scope*'. Before deciding, further information was gathered on i) the approach of other metal consortia and ii) the speciation of the Rh(III) compounds.

The TE agreed that speciation is a more important determinant / predictor for mutagenic effects than solubility (as determined by e.g. bioelution).

Based on the available data, the TE proposes to:

-classify Rh(III) trichloride, trinitrate, sulphate, acetate and triammonium hexachlororhodate as Muta2 (cfr. positive in vitro and in vivo testing)

-classify diammonium sodium hexakis(nitrito-N)rhodate as Muta2; there is negative in vivo testing data available, but the compound is expected to transform in mutagenic species upon dissolution in acidic medium. The substance will be registered by 1 company, is an intermediate, but the company supports the classification for precautionary reasons.

-not classify Rh metal for this endpoint.

ACTION:

- **Bibra to update the ITS and IUCLID as appropriate, w.r.t. these genotox classification decisions.**

For the poorly water soluble Rh(III) compounds (Rh(III) trioxide, trihydroxide, triiodide and tris(2-ethylhexanoate)), it is not possible to decide today -using all available evidence- on their mutagenic potential.

The TE recommends to:

-perform AMES tests on the 3 compounds which have not been tested before (not the triiodide) to check their mutagenic potential

-develop a good strategy for further in vivo testing (included via testing proposals) after considering:

°the chemistry and speciation of the compounds

°an internal review of the available data.

This proposal should allow a scientifically supportable selection of test assays and test substances and/or direct read-across of the Muta2 classification.

PGM nanomaterials

If PGM substance(s) are proven to be nanomaterial, the respective registration dossier(s) will be updated (>2017). It is proposed to wait for effective characterization (and thus deciding on the nano-character) till the appropriate definitions and methodologies are included in the legislation. It is suggested to check the PGM blacks for meeting the nano-definition.

3. PNEC and DNEL derivation

1. PNEC derivation

The PNECs for Pd have been derived and entered in IUCLID and the Generic Environmental Risk Assessment. No remarks from the TE.

The PNECs for Rh have been drafted by WCA, and will be circulated to the members soon.

The PNECs for Pt (<30 June) and Ru (<August) will be derived when the ecotox testing is finalized (the Pt PNECs will be update -if required- after finalization the KC ecotox testing).

2. DNEL derivation

Pd genotox

Pd has a complete negative genotox dataset (in vitro and in vivo), and no testing and/or classification is proposed by Bibra.

For the Pd tetraammines, the existing AMES test lacks a bacterial strain susceptible to oxidative mutagenesis or cross-linking agents, and this test is therefore not in line with the ECHA testing requirements. Pd tetraammines are not expected to cause oxidative damage, and the TE consider the database and the proposal to not classify conclusive.

The TE proposes to

-keep this test/endpoint in 'as is' (do not perform a new AMES test)

-wait for further input from ECHA prior to launch a new test.

ACTION:

- **Bibra to include some additional wording in the study record to explain the missing information is unlikely to change the hazard conclusions (<30 June 2016).**

Pd DNELs

The DNELs are derived using the ECHA assessment factors, except for the allometric scaling factor (rat -> human) of 4 which was not applied as considered already being covered (except for Pd di(4-oxopent-2-en-2-oate) where factor 4 is retained for unknown effects of anion). Many Pd DNELs were higher than the nuisance dust limits (10 mg/m³), and this value of 10 mg/m³ is used for the corresponding occupational risk assessment. From industrial experience, there are no empirical evidence for respiratory sensitization following inhalation exposure to skin sensitizing Pd compounds; the qualitative hazard conclusions have been lowered from 'high' to 'moderate'. This can still be considered too conservative for some compounds.

The TE recommends to check which endpoint is driving the conclusion and revise is appropriate.

ACTION:

- **Bibra to check what hazard endpoint is used for the proposed qualitative hazard bandings, and lower where appropriate (June 2016).**

Pt genotox

There is a complicated dataset for Pt genotoxicity. For the in vivo data for tetraamminePt dinitrate:

- the UDS is only relevant if positive and

- the micronucleus testing is only relevant if toxicokinetic and site of contact information is available.

Only the Drosophila data remain as reliable evidence. Key questions to address for further testing is 1) what assay to choose and 2) what substance to test.

As only partial data are available (not conclusive), the proposal is to not classify the Pt group substances (Pt(II) and Pt (IV)) for genotox until reliable in vivo evidence gets available (to be included via testing proposal in registration dossier). **This proposal is supported by the TE.**

ACTION:

- **Bibra to closely check the complete Pt genotox database (15 June 2016)**

The TE proposes to

-have the complete dataset reviewed by an external expert to better define the genotoxicity profiles of representative Pt series substances, and where the key data gaps exist, and

-to obtain recommendations on the appropriate in vivo assay(s) in respect of any TP.

This review should allow a scientifically supported testing proposal strategy to be included in the Pt(II) and Pt(IV) registration dossiers. Depending on regulatory acceptance, we have to review and/or update the classifications at a later stage.

The TE acknowledges that the decisions of regulators on this specific topic is unpredictable. For instance, they may draw a link with the 'platins' (potent mutagens, probable carcinogens) – which are specifically designed to interact with genetic material and have differing ligand and bioactivation behaviour than the Pt(II)/(IV) substances to be registered. Examination of the genotoxicity outcomes from the PMC programs can form part of the expert review to see if such a linkage can be preempted.

3. PMC approach for chloroplatinates ('ClPt') occupational exposure assessment

Respiratory sensitization is a local effect for DNEL derivation.

The ACGIH OEL of 2 µg/m³ for soluble Pt (expressed as Pt) and 1 mg/m³ for Pt metal are applied by most PGM companies worldwide. It was mentioned that REACH formally requires a substance specific value – a clear explanation needs to be added if a different approach/value is used. The underlying hazard to derive the DNELs from often differs between compounds.

ACTION:

- **JM/Bibra to provide to EBRC a brief explanation what hazard is driving the Pt DNEL**

It is anticipated that the regulators will re-iterate the OEL derivation soon after registration. The German 'ERB-concept' ('Exposure-Risk-Relationship') is used for non-threshold carcinogenic substances, but it can be considered to use the principles behind this concept to come up with a value for the chloroplatinates. The qualitative approach is recognized to be a temporal solution, and a threshold will need to be available on the mid-to-long term. The next IPA epidemiology study (still to be initiated) will be limited compared to the Heederick et al (2015) study. From the Heederick et al study, one low residual risk estimate placed a tolerable benchmark value in the region of 20-60 ng/m³, though it cannot be considered as fully robust. If a DMEL were to be derived from this non-robust estimate, due to the application of uncertainty factors the DMEL would place in the pg/m³-range.

It is mentioned that providing DNELs triggers the requirement to derive RCRs. As described in ECHA Practical Guidance 15 (Nov 2012): if the RMMs for ClPt respiratory sensitization (non-threshold) are deemed to be protective for the other toxic routes (for which DNELs are derived) as well, adequate control of workers'safety via these toxic routes should be appropriately justified and/or documented. Safe use is then ensured when complying with the prescribed RMMs. BASF has used the qualitative approach in 2 dossiers, and they will check if these dossiers have ever been checked by regulators. BASF is willing to share this information with the PMC TE

ACTION:

- **BASF to share the relevant CSR sections as an example for a qualitative approach for occup. exposure/risk assessment with PMC Tox Experts**

The ClPt subgroup will meet in a face-to-face meeting to discuss further on this specific topic.

ACTION:

- **JM to check availability of Steven V (chair of the sub-group) and inform with sub-group members for most suitable date via doodle.**

4. Occupational Monitoring project: status

For the Pt and Pd group substances, dermal DNELs have been derived, but there is currently a lack of occupational monitoring data. Skin wiping is included in the HERAG Factsheets as an appropriate approach, and has been applied for other metals before (Sb, Ni, Zn). If no monitoring data are available, we might face RCRs>1 for Pt substances, and alternative approaches have to be investigated.

The TE encourages companies to provide/share dermal exposure data with PMC secretariat if available.

The TE suggest to consider gathering occupation dermal exposure data in a follow-up project, and not include in the current monitoring project.

It was discussed whether the current Occupational Monitoring project should focus on the inhalable and/or respiratory fraction. The hazard assessment is the driver to decide what fraction should be sampled for occupational inhalation monitoring. **The TE advises to monitor at this stage only the inhalable fraction.** IRAS (on behalf of IPA) will start a project to compare the inhalable vs respiratory fraction for Pt group substances, which might provide insight in how these to fractions relate (or not).

5. AOB, next meetings/calls and closing remarks

Next PMC BtB meetings will be organized 4-6 October 2016 in Brussels.

Annexes

Annex I: Agenda

1. Welcome and Introduction

1. Confidentiality and Competition Law
2. Tour de table and apologies
3. Approval of the agenda
4. Approval of the minutes of previous meeting, status of action points

2. PGM testing programme

1. PGM phys.-chem. Testing
   1.1. Outstanding tests of new solids
2. PGM ecotox testing
   2.1. Karstedt: Hydrolysis & further ecotox testing
   2.2. HHPA-2AE
3. PGM HH testing
   3.1. Karstedt and HHPA-2AE
   3.2. Tetraammines genotoxicity
   3.3. RuCl3 and TetradoRu
   3.4. Rh(III) genotox classification

3. PNEC and DNEL derivation

1. PNEC derivation
2. DNEL derivation
   2.1. Pd – final DNELs
   2.2. Chloroplatinates: update and brainstorming
   2.3. Other Pt DNELs
   2.4. Read across approach
3. Exposure/risk assessment ENV/HH for Pd – final discussion
4. “Man via environment” assessment

4. Occupational Monitoring project: status

5. AOB, next meetings/calls and closing remarks

Annex II: participant list

Roland Brasch, Heraeus (Germany)

Arno Buthe, Heraeus (Germany)

Maxime Eliat, Arche (Belgium)

Olga Duerr, BASF (Germany), by conference call

Herbert Fuchs, Heraeus (Germany)

Mark Hosford, Johnson Matthey (United Kingdom), by conference call

Jelle Mertens, EPMF (Belgium)

Mark Raffray, Consultant (United Kingdom)

Nissanka Rajapakse, johnson Matthey (United Kingdom), by conference call

Klaus Rothenbacher, EPMF (Belgium)

Jutta Schade, EBRC (Germany), by conference call

Michael Shepherd, Vale (United Kingdom)

Michael Thiel, BASF (Germany)

Steven Verberckmoes, Umicore (Belgium)

Daniel Vetter, EBRC (Germany)

Pete Watts, BIBRA (United Kingdom), by conference call

Richard Young, BIBRA (United Kingdom), by conference call

Annex III: Slides presented at the meeting

Cfr handouts