PGM WG&TE meeting

Draft minutes, Brussels, 14 March 2018 (10:30-16:45)

Chair: Michael Thiel (BASF, Germany)

Co-chair: Arno Buthe (Heraeus, Germany) (Approved during the meeting)

ACTIONS	Who ?	When?	Status
Update OFI trackers as proposed and agreed (Pd, Pt, Rh and Ru group substances)	PMC	ASAP	
Perform approved actions from the OFI tracker	PMC	Cfr. proposed timings in OFI	
Consult internally on PdO and Rh2O3 testing for oxidizing properties	Companies	<31 March	
Organise testing oxidizing properties (if no objections or (reference to) existing test data are received	PMC	April '18	
Check internally the relevance & express support to update the proposed AnnexIII dossiers.	Companies	<15 April	
Include update AnnexIII dossiers to AnnexVII dossiers (Pd, Pt, Rh, Ru and Ir group substances) in 2019 workplan & budget	PMC	<June GA meeting	
Check internally which technique can be used for palladium speciation	Companies	<31 March	
Update Pt nitrate dossier to include TP for in vivo genotox	PMC		***Done***
LR to submit Pt nitrate dossier	Heraeus		***Done***
Inform ECHA about inclusion TP in Pt nitrate dossier	PMC	ASAP after dossier update	***Done***
Communicate with ECHA about the Pt testing approach	PMC	tbc	
Develop a testing stategy for in vivo genotoxicity testing	PMC & companies	Q2-Q3 2018	
Organise Pt in vivo genotox testing	PMC & companies	<Q2 2019 (anticipated timing)	

Perform Pt in vivo genotoxicity testing	PMC	ASAP after ECHA approval (Q2 2019?)	
Inform members about the discussions with ECHA (meeting 15 March)	PMC		***Done***
Draft RA justification reports for HHPA group, incl. experimental testing	PMC & companies	<end 2018	
Update/finalise dirhodium trisulphate and rhodium tris(2-ethylhexanoate) dossiers	PMC	April 2018	***Done for Rh2(SO4)3 dossier***
Check pH Rhodium trichloride hydrate	Companies	<15 April	
Draft TP for in vivo genotoxicity for rhodium trisulphate and include in the dossier	PMC	ASAP	
LR to submit rhodium trisulphate dossier	Umicore	ASAP once available	
Schedule a call and discuss about RhI3 solubilisation and speciation.	PMC and Johnson Matthey	Q2 2018	
Check ecotox data Ru(III) cmpds and order an acute ecotox test with the most sensitive species for tris(nitrato-O)nitrosylruthenium to confirm RA + add 10K euro to the 2019 budget.	PMC	Test to run in 2019	
Update iridium metal dossier from AnnexIII to AnnexVII + order bioelution testing	PMC	2019	
Check if dossiers of rhenium and gold group are candidate for update Annex III to VII	PMC	<June GA meeting	

The minutes summarise the discussions and decisions taken during the meeting, and need to be consulted in parallel with the slides as presented (and made available) to the participants.

1. Welcome and Introduction

Michael Thiel welcomed the participants reminding the anti-trust and competition law guidelines. The meeting started by a tour de table (see list of participants in annex 1).

The agenda of the meeting has been approved. The non-metal specific actions of previous meeting (18 October 2017) have been reviewed and the draft minutes have been approved.

Arno Buthe (Heraeus) is candidate to become co-chair of the PGM TE/WG. This proposal is approved by the participants.

2. Palladium and compounds

2.1 Status action points Autumn BtB meeting 2017 (incl. agreed testing Pd compounds)

The actions of previous meeting (18 October 2017) have been reviewed. Most of the agreed testing (incl. 3 RDT/Reprotox screening assays) has been initiated, and test samples are under preparation or have been send to the contracted CROs.

2.2 Review of the OFI tracker, setting priorities for 2019 + budget 2019

The OFI tracker is reviewed. The members agree with the proposals made, including to

-not test Pd(OH)2 for eye irritation/corrosion and keep the classification as Eye Dam1 (the entry can be removed from the OFI)

-not precautionary classify PdO for oxidizing properties, due to the uncertainty of the applicable classification category and consequences for transport. The PMC secretariat will prepare an email for the members to allow internal discussions and provide additional input. Responses are due 26 March COB. If no objection is received, the test (UN test O1, covering transport regulation and CLP/GHS) can be performed. The same reasoning applies to Rh2O3.

The proposed updates of the dossiers of Palladium acetate, Palladium sulphate, tetraamminepalladium nitrate and tetraamminepalladium dihydroxide from Annex III to VII, and the associate additional testing, have been approved for the 2019 workplan&budget

The members agree that an update of the read-across (RA) justification documents is required when the ongoing test program is finalised, and the dossiers are being updated accordingly. In line with the update for the TAPt dossiers & RA documents, (experimental) justification of speciation to the same toxicologically active species‘ and absence of counter-ion-effects‘ is required for the 4 RA groups. For chemical speciation, Raman is identified as an alternative to NMR (which is not suitable for Pd). The

companies will check internally what other technique is applicable. If no suitable alternative is identified, an external chemistry expert can be contacted.

An expert review is currently being performed by DHI on one dossier of the TAPd group, tetrachloroPd group and hexchloroPd group. The complete dossier will be reviewed, including RA. The report is expeced end Q2 – early Q3.

The draft budget is approved.

ACTIONS:

-PMC to update OFI tracker as proposed and agreed
-PMC to send reminder to members on testing PdO and Rh2O3 for oxidizing properties. If no objections or (reference to) existing test data are received, the samples for oxid properties can be ordered.
-PMC to include update 4 AnnexIII dossiers to AnnexVII dossiers in 2019 workplan & budget
-companies to check internally which technique can be used for palladium speciation (cfr email sent by PMC secretariat).

3. Platinum and compounds

3.1 Status (ongoing) registration dossiers & updates

An update was given on the registration status. All Pt dossier have been registered by the Lead Registrants.

3.2 Status action points Autumn BtB meeting 2017 (incl. agreed testing Pt compounds)

The actions of previous meeting (18 October 2017) have been reviewed. The agreed testing (incl. 1 RDT/Reprotox screening assays) has been initiated, and test samples are under preparation or have been send to the contracted CROs.

3.3 Pt genetox: Status discussions with ECHA and testing

All Pt dossiers, incl. the Testing Proposals (TP) for in vivo genotoxicity where required, have been submitted by the LR. For Platinum dinitrate, the participants agree to include a testing proposal for in vivo genotoxicity instead of the current waiver. The dossier will be updated by the PMC Secretariat, send to the LR for registration, and ECHA will be informed about this update (cfr. discussion with ECHA on grouped Pt genetox assessment).

The participants were updated on the status of the ECHA Draft Decisions received for the two Umicore Tetraammineplatinum NONS dossiers. The updated RA documents were considered plausible by ECHA, and might serve as an example for the other RA documents to be updated.

The public consultations (PC) of the TP included in 3 PMC Pt dossiers have been launched and run till 16 April 2018. This PC is not intended for input from PMC or its members. The PC for the remaining Pt TP are expected soon.

For Pt genetox testing, test sample purity needs to be properly verified and/or tested to avoid false positive responses.

Mark Hosford presented the status of IPAs in vivo genotoxicity testing program. The IPA drivers for performing in vivo genetox testing (a.o. product stewardship, image implications) are different from PMC (REACH focus), and the IPA substance portfolio differs from the PMC one. Based on in vitro protein reactivity testing of various Pt compounds (assessed via the DPRA assay), the IPA developed the hypothesis of a bell-shaped curve-behaviour of expected genotoxicity potential versus protein reactivity, whereby Pt compounds with a very high protein reactivity (like chloroplatinates) are predicted to show low genotoxicity potential in vivo. Only Pt compounds with intermediate protein reactivity and sufficient bioavailabilty are predicted to be of concern for genotoxicity (like platins). The IPA has discussed this hypothesis with David Kirkland, who considered it a plausible theory and approach for setting up in vivo genetox testing. The IPA identified cisplatin as a suitable positive reference material for testing the hypothesis, but has not been able to identify a proper negative reference material (stable and well defined composition, bioavailable, non-mutagen, limited commercial risk…). The combined in vivo Comet/MN assay is the proposed assay by IPA (cfr. details mentioned on slide 42). Kidney is suggested as additional target tissue, and germ cells are not included (cfr. short exposure time). Before initiating the testing, sufficient information needs to be available on the test compound and its behaviour (like TK data, in vitro genotoxicity profile, DPRA response).

[*Post meeting note: the DPRA work is performed at a university lab, and will be published in a peer-reviewed journal*.]

The IPA presentation/testing approach and the overlaps/differences with the PMC approach (driven by REACH) have been discussed at length. It was stressed that test substance selection and identification are critical, as well as the selection of the test lab (experience with genetox testing, availability of historical control data), study design and prioritisation of test substances (tiered approach if allowed by ECHA). All participants agreed that a tiered testing approach should be aimed for. This tiered testing approach needs to be driven by an intelligent testing design, whereby

-test substances need to be well-considered and should ideally allow testing the hypothesis of protein reactivity vs genotoxicity potential, and

-learning lessons of the first assay allow refinement and optimisation of the test design of the following assays.

At this point in time, without having the in vivo data available and without having proof-of-concept for the protein reactivity hypothesis, the participants could impossibly judge if the tiered testing approach could

also imply potential avoidance of testing. The possibility to avoid animal testing will only become evident as the experimental in vivo data get available. If a tiered approach is allowed by ECHA, sufficient time is needed (6-9 mths for a single test, eventually shorter if all testing is ordered at the same lab and can be performed sequentially). Parallel testing of the 5 REACH RA groups at a single lab is considered impossible and not advisable.

It was considered essential that the IPA and PMC merge views on Pt genotoxicity, and speak with a single voice. This is especially relevant for communication to regulatory bodies like ECHA, where the PMC is considered the most appropriate body to communicate and to organise the testing considering its REACH focus and good contacts at ECHA. The participants agreed that the PMC is in the driving seat to develop a testing strategy, communicate with ECHA, and perform the in vivo genotoxicity testing for its substances under REACH. The IPA will postpone its testing accordingly, and will fill the data gaps afterwards with subsequent in vivo genetox testing, where needed. The IPA is available for technical support when drafting a study plan/argumentation…

France has a meeting at ECHA 15 March, a.o. on the Pt genetox testing. The participants ask to be updated on the discussions/outcome of the meeting.

ACTIONS:

-PMC to update Pt nitrate dossier to include TP for in vivo genotox, LR to submit the dossier ASAP and PMC to inform ECHA about this update.

-PMC to communicate with ECHA about the Pt testing approach, to develop a testing stategy for in vivo genotoxicity testing and organise/perform the testing.

-PMC to inform the members about the discussions with ECHA on 15 March

3.4 Review of the OFI tracker, setting priorities for 2019 + budget 2019

The OFI tracker is reviewed. The members agree with the proposals made, and to remove the entries for

-Karstedt PBT assessments + KC dossier updates as suggested by Bibra, and

-inclusion the the additional in vitro geneotox assay with TAPtCl2 from the OFI tracker.

All these actions have been performed and included in the updated dossiers where required.

The proposed update of the dossier of tetraammineplatinum dichloride from Annex III to VII (no testing anticipated) has been approved for the 2019 workplan.

For the anticipated in vivo genotoxicity testing for the HHPA read-across group (incl. HHPA and HHPA-2AE), a RA justification needs to be drafted, including an experimental verification that both speciate to the same toxicologically active species and absence of any counter-ion effects. A similar experimental setup to the earlier TAPt-group testing is approved. The analysis (195Pt NMR) can be ordered at an external lab (like Aqura).

[*Post-meeting note: so far, no RA justification report has been drafted for the HHPA RA group. For the Pt group substances, RA justification reports have been drafted for the group of hexachloroplatinates and tetraammine*Pt *compounds*).]

An expert review is currently being performed by DHI on one dossier of the hexchloroPt group. The complete dossier will be reviewed, including RA. The report is expeced end Q2 – early Q3.

The budget for the KC EOGRTS (800K euro) is likely too high, but the participants agree to keep this number in the 2019 budget.

ACTIONS:

-PMC to update OFI tracker (remove completed entries)

-PMC to perform actions as proposed in the OFI tracker

-PMC to include update tetraammineplatinum dichloride from Annex III to VII in 2019 WP

-PMC&companies to draft RA justification reports for HHPA group, incl. experimental testing

4. Rhodium and compounds

4.1 Status (ongoing) registration dossiers

An update was given on the registration status. All Rh dossier have been successfully registered by the Lead Registrants, except dirhodium trisulphate and rhodium tris(2-ethylhexanoate).

The dossier for dirhodium trisulphate was rejected during the ECHA Manual Completeness Check for SID reasons. The SID has been reviewed (mono-consituent substance meeting 80-20 rules), some additional data for phys-chem have been included, and the dossier is under review/approval and expected to be re-submitted before end March 2018.

The final phys-chem assays for rhodium tris(2-ethylhexanoate) (composition in 2-ethylhexanoic acid) are currently running, and the ones for the composition in 2-ethylhexanol have been finalised. The SID has been updated as well (mono-consituent substance meeting 80-20 rules). The dossier is expected to be ready for review/approval end March, and submission by the LR early April.

ACTIONS:

-PMC to update/finalise dirhodium trisulphate and rhodium tris(2-ethylhexanoate) dossiers ASAP to be available for LR registration in April at the latest.

4.2 Status action points Autumn BtB meeting 2017 (incl. agreed testing Rh compounds)

The actions of previous meeting (18 October 2017) have been reviewed. Most of the agreed testing has been initiated, and test samples are under preparation or have been send to the contracted CROs.

The discussion and actions related to the oxidising properties testing of Rh2O3 is included under point 2.2.

4.3 Review of the OFI tracker, setting priorities for 2019 + budget 2019

The participants agree with the proposals made in the OFI tracker.

For update of Annex III to VII, the PMC secretariat proposed Rhodium trichloride hydrate, Dirhodium trisulphate, Tris(triphenylphosphine) rhodium (I) chloride, Carbonyl(pentane-2,4-dionato-O,O')(triphenylphosphine)rhodium and Carbonyl(pentane-2,4-dionato- O,O')rhodium as most relevant candidates. Except for Dirhodium trisulphate, additional testing is anticipated for all proposed dossiers with a total cost of approx. 120K euro. For Rhodium trichloride hydrate, the companies are requested to check the pH of this substance as this might be the basis to fill the data gap for skin sensitisation testing with a waiver. Although most of the participants support a gradual update of AnnexIII to VII dossiers, some have a different internal policy to avoid animal testing if not strictly required. The participants are therefore requested to check internally the relevance to test & update, and express support for updating the proposed AnnexIII dossiers to AnnexVII dossiers for the Pd, Pt, Ru, Rh and Ir-groups.

The PMC members agreed in previous meetings already to include a TP for in vivo genotoxicity for water soluble Rh(III) compounds. As test substance, no agreement has been reached yet. There were 3 candidates, based on the genetox testing profiles and the PMC portfolio: Rh acetate (UVCB), triammonium hexachlororhodate (removed from PMC scope since early 2018) and Rh sulphate. For the reasons mentioned in brackets in previous paragraph, Rh sulphate is approved as test substance. Referring to SID and industrial manufacturing, the decision to test a solid or solution form will be taken later, and this should thus not be specified in the TP. The TP can be drafted, included in the dossier, and updated by the LRs. The assay is similar to those proposed for platinum.

The AMES testing for the poorly water soluble Rh(III) compounds is ongoing. First results with Rh2O3 confirm the absence of genotoxic potential of Rh(OH)3.

The solubilisation/speciation testing of RhI3 in water vs DMSO is still pending. NMR is considered not sufficiently sensitive, and an alternative technique might be needed. JM might be able to perform this analysis, and proposed to have a bilateral discussion JM experts/PMC to discuss further and see what's possible.

The draft 2019 budget might be changed depending on the responses related to AnnexIII dossier updates.

ACTIONS:

-Companies to check internally the pH of Rhodium trichloride hydrate

-Companies to check internally the relevance & express support to update the 5 proposed Rh dossiers.

-PMC to draft the TP for in vivo genotoxicity and include in the Rhodium trisulphate dossier.

-LR to update the relevant dossier afterwards.

-JM/PMC Secretariat to schedule a call and discuss about RhI3 solubilisation and speciation.

5. Ruthenium and compounds

5.1 Status (ongoing) registration dossiers

An update was given on the registration status. All Ru dossier have been successfully registered by the Lead Registrants, and the Tris(nitrato-O)nitrosylruthenium dossier has already been updated upon request of a co-registrant (higher purity required than in original dossier).

5.2 Status action points Autumn BtB meeting 2017 (incl. agreed testing Ru compounds)

The actions of previous meeting (18 October 2017) have been reviewed. Most of the agreed testing has been initiated, and test samples are under preparation or have been send to the contracted CROs.

5.3 Review of the OFI tracker, setting priorities for 2019 + budget 2019

The participants agree with the proposals made in the OFI tracker. For RuAc, the participant agree that formal access to the RDT study (via a LtU) is not required, as this is no formal data requirement. The outcome of this RDT study is included in the dossier via reference to the TSCA notification of this study, and the review performed by M Raffray (the study does not trigger additional classifications or testing). This entry can be removed from the OFI tracker.

For update of Annex III to VII, the PMC secretariat proposed ruthenium acetate (no datagaps) and tris(nitrato-O)nitrosylruthenium. For the latter substance, it is unclear if RA from other Ru(III) compounds is possible. Therefore, the participants agree to perform an additional acute ecotox test with the most sensitive species (based on the already available ecotox data with Ru(III) cmpds). The appropriate budget needs to be included for 2019.

ACTIONS:

-PMC to update OFI tracker (remove completed entries)

-PMC to check ecotox data Ru(III) cmpds and order an acute ecotox test with the most sensitive species for tris(nitrato-O)nitrosylruthenium to confirm RA. Add 10K euro to the 2019 budget.

6 Iridium and compounds

6.1 Review of the OFI tracker, setting priorities for 2019 + budget 2019

For update of Annex III to VII, the PMC secretariat proposed iridium (metal) and diammonium hexachloroiridate. For iridium, a similar approach than the other metals is proposed, but the required bioelution data are missing (TDp data are available). The members approve this update and the associated bioelution testing (estimated at 15K euro). For diammonium hexachloroiridate, no data are availabe (except a potential RA for acute tox (oral) from dihydrogen hexachloroiridate). The cost to update is estimated at 50K euro. The members will check internally if this update is required/supported.

It was asked by the participants if other updates are required, like for the Rhenium and Gold group substances. This will be checked by the PMC secretariat, and included in a next discussion.

ACTIONS:

-PMC to update the iridium file to AnnexVII

-PMC members to verify the relevant / support to update diammonium hexachloroiridate to AnnexVII

-PMC to check if dossiers of Rhenium and Gold group are candidate for update to Annex VII

7. Workplan and budget 2019

The draft budget for 2019 has been presented in more details. No additional remarks were made on top of those already mentioned in the previous paragraphs.

8. AOB, next meeting, closing remarks

The GA spring meeting is scheduled 5-6 June in Liege (Belgium)

The BtB autumn meeting is scheduled 9-11 October in Brussels.

Annex 1: Participants

Bodo BERKNER, Ferro (Germany) – *by conference call*

Roland BRASCH, Heraeus (Germany)

Arno BUTHE, Heraeus (Germany)

Maxime ELIAT, EPMF (Belgium)

Herbert FUCHS, Heraeus (Germany)

Mark HOSFORD, IPA

Michael HUBER, C. Hafner (Germany)

Mari JARVIKIVI, Norilsk (Finland)– *by conference call*

Marie-Laure LEDRICH, Traxys (Luxembourg) – *by conference call*

Olga LEMKE, BASF (Germany) – *by conference call*

Jelle MERTENS, EPMF (Belgium)

Nissanka RAJAPAKSE, Johnson Matthey (United-Kingdom)

Christoph RÖHLICH, Heraeus Deutschland (Germany)

Dorothea STEIGER, Heraeus (Germany)

Hege STUBBERUD, Glencore (Norway)

Michael THIEL, BASF (Germany)

Steven VERBERCKMOES, Umicore (Belgium)

Paul YLIOJA, Johnson Matthey (United-Kingdom)