PGM WG&TE meeting

Minutes, Brussels, 9 October 2018 (11.00-15.45)

Chair: Michael Thiel (BASF, Germany)

Co-chair: Arno Buthe (Heraeus, Germany)

ACTION	WHO?	WHEN?
Check internally which technique can be used for palladium speciation	Companies	<21 October 2018
Include Exposure Scenios in Chesar and link OC/RMM to standard phrases (ESCom catalogue)	EPMF secretariat	Cfr tiered approach slide 11
Draft MISA workplan with actions agreed during meeting	EPMF secretariat	<15 November 2018
Rediscuss update PGM metal dossiers to replace current waivers based on bioelution data	EPMF secretariat + companies	1 April 2019 (spring BtB meeting)
Communicate about classificatoin PdO and/or Rh2O3 for oxidizing properties (if required)	EPMF secretariat	After receipt testing report
Check if effects in DRF PdCl2 are not palatability effects, and gavage should be used instead.	EPMF secretariat & RSA	<end Oct 2018
Draft justification document for direct in vivo skin sensitization testing (and not in vitro as first tier)	Johnson Matthey	<end Nov 2018
Agree on dosing for full OECD422 assay with Pdacac	EPMF secretariat+companies	<21 October 2018
Decide to continue RDT/Repro screening assay with PtN	EPMF secretariat+companies	once PtN SID/ sameness is clarified
Finalise RAJR HHPA group + send to members for review	EPMF secretariat+companies	<end Oct 2018
Send PtN test samples to Evonik for 195Pt NMR analysis	PtN registrants	<21 October 2018
Develop manufacturing process/reaction scheme for PtN	PtN registrants	once PtN SID/ sameness is clarified

Inform with candidate testing labs for iv mutagenicity testing on price + experience with metals	EPMF secretariat	<end Nov 2018
Check internally on other candidate labs for iv mutagenicity testing + inform about preferred testing lab	companies	<end Oct 2018
Inform EPMF secretariat about agreement renaming Karstedt Concentrate to *‚1,3-diethenyl-1,1,3,3-tetramethyldisiloxane and its platinum(0) complexes*‘.	KC registrants	<21 October 2018
Karstedt Concentrate LR to update dossier	Heraeus	<end Oct 2018
Update KC SID card following dossier updates	EPMF secretariat	<end Nov 2018
Draft RAJR for Rh(III) mutagenicity and have TP+RAJR reviewed by Mark Raffray	EPMF secretariat + Mark Raffray	<end Nov 2018
Check if RhI3 dissolution work can be done in house	Companies	<end Oct 2018
Perform RhI3 dissolution work by company or in external testing lab	EPMF secretariat	<end 2018
Review proposal for additional TD testing of organic metal salts vs organometals	Companies	<21 October 2018
Include budget for additional TD testing in 2019 budget	EPMF secretariat	<end Oct 2018
Inform EPMF Secretariat if nanoPGMs need registrations under REACH	Companies	ASAP and at latest <end 2018

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 *(11-11.30)*

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).
The agenda of the meeting has been approved.
The status of the action points of the spring BtB meeting have been reviewed. Some are not finalised, but come back later in the meeting for further discussion/development.
The draft minutes of the spring BtB meeting have been approved.

2. PGM exposure scenario workplan: inclusion exposure scenarios in Chesar

The workplan for inclusion of the exposure scenarios in Chesar was presented. This work allows/facilitates direct incorporation in the company eSDSs, and improve readability of the ES.

A tiered approach is proposed, starting with those substances for which the ES are already (partly) available in Chesar (tier1), then those for which ES are not yet available in Chesar and where no direct changes in the ES are expected (tier2), and ending with those for which ES are not yet available in Chesar and where changes in the ES are expected due to ongoing/planned work (tier3). Substances registered above 10T that are not classified are not included in this exercise, as no ES are drafted for these. The silver substances will be included at a later stage due to the ongoing work on environmental and human health hazard. **The participants agreed with the proposed approach and list of substances per tier**.

3. First MISA workshop : key conclusions / learnings *(11.30-11.45)*

The participants were informed about the some key findings from the first MISA workshop focussed on selected human health topics (read-across, EOGRTS/route of exposure and mutagenicity). Most important learnings were that:

- Bioelution can be used in a qualitative way for grouping/read-across, but not to fill endpoints or waive formal data requirements.
- Bridging studies should be used on top of bioelution data (if available) to strengthen read-across with experimental data. For Annex IX-X substances, this is typically be done with 28-d RDT studies, or their DRF studies. For Annex VII-VIII substance, this is less relevant as 28-d RDT studies are the highest tier formal data requirements. Alternatives are acute tox studies, available RDT studies or via DRF studies.

- From experience, regulatory acceptance of read-across is difficult to obtain, unless proven by sufficient experimental data and justified according to all RAAF criteria. Metabolomics data can be useful in this perspective.
- Data requirements for nanos, as part of a ‚bulk form' registration dossier (eg. nanoAg as part of Ag metal dossier), will most likely be triggered by the merged tonnage of nano+bulk form, and not by the tonnage of the nanoform itself [*this has been confirmed by the EU COMM participant to the MISA workshop after internal discussions*].
-

A workplan for the PGMs will be drafted and submitted to ECHA, based on the learnings from the workshop (deadline 15 Nov 2018). Key actions are:

- Review dossiers for use of bioelution. This is especially relevant for the PGM metal dossiers, where formal data requirements are waived because of substance inertness, as shown by bioelution. This is not considered sustainable, and the endpoints should be filled with data instead. The **proposal** is:
  - Investigate grouping / read-across possibilities (eg metal with poorly soluble metal oxides).
  - Wait data generation from current test program (ie, update PGM oxide dossiers from AnnexIII to regular AnnexVII dossiers).
  - Wait finalisation of ongoing literature review (ENV+HH) for PGM metals+nanoforms.
  - Rediscuss during 2019 spring BtB meeting, schedule additional testing (if required) and dossier updates for 2020
- Review Read-Across and the respective justification reports (or draft if not yet available) to fulfull all requirements as listed under RAAF.

The participants agree with these actions.

4. Palladium and compounds *(11.45-12.15)*

4.1. Update ongoing testing

A short update was given on the various testings that are ongoing:

- Pd ecotox refinement: algae testing finalised, Daphnia reproduction and ASRIT assays ongoing. The next steps (revision read-across strategy? futher testing?) will be discussed once all data are available.
- PdO: - bioelution testing ongoing
  - oxidising properties being tested and shown to act as strong oxidizer. There is a chance that a classification as oxidizing solid is required. This will be communicated to the membership once confirmed.
- PdCl2:
  - genotox testing: AMES and in vitro MLA assays have been finalised, and showed absence of mutagenic activity
  - a preliminary 5-day test has been performed to confirm test substance identity and justify the proposed dosing regime of 1000-3000-10000 ppm in diet. The DRF in-life phase has been completed (to be followed by OECD407-421 assays). The high-dose male animals were terminated at test day (TD) 9. All other animals were terminated as scheduled. Test item stability, and diet concentration/homogeneity analysis is ongoing. For test item stability, FT-IR is

not suited as no useable spectrum of the pure test item can be obtained. Raman analysis was proposed instead. It was questioned if the effects were not a palatability effect, and if gavage would not be a better option if corrosive effects are unlikely. The effects at the high dose level were questioned to be test item related. Also, the observations like dark content in caecum/colon might reflect test item presence rather than a test item effect.

- Tetraamminpalladium dichloride:
    - Ames assay showed absence of mutagenic activity
- Disodium tetrachloropalladate:
    - in vivo skin sensitisation testing scheduled and reporting expected soon. For skin sensitisation, a WoE statement needs to be drafted for directly testing in vivo rather than in vitro. The participants referred to an ECHA guidance document, the recent Kimber publications and other publications on eg the DPRA assay to justify why in vitro testing is not appropriate/conclusive for metals. Johnson Matthey proposed to draft a justification, after which it will be reviewed/complemented by the other members.
    - The DRF in-life phase has been completed (to be followed by OECD407-421 assays). The dosing regime was 1000-3000-10000 ppm in diet. All animals were terminated as scheduled. Test item stability (FT-IR), and diet concentration/homogeneity analysis is ongoing.
- Pdacac:
    -DRF for the OECD422 assay has been finalised (gavage, corn oil as vehicle). Dosing regime was 0-100-300-1000 mg/kg/d. Mid and high dose animals have been terminated at TD6 for animal wellfare reasons. For the low dose animals, one female died at TD8. The other low-dose animals recovered bodyweight since TD8, and were exposed for 14d as scheduled. Test item stability has been shown, and test item concentration/homegeneity is confirmed.

    [*post-meeting notes:*
        -the diet concentration/homogeneity report arrived the day before the meeting, and analytics reassured correct dosing / homogeneity.
        -an email has been send to the Tox Experts to agree on a dosing regime for the full test]

4.2. Expert review Registration dossiers Pd/Pt

DHI, as an external consultant, has reviewed teh registration dossiers of the hexachloroplatinates, hexachloropalladates, tetrachloropalladates and tetraamminepalladium compounds. Remarks/suggestions were made on various points, but most of these are already included in the OFI tracker and will thus be gradually tackled in the respective dossiers.

5. Platinum and compounds *(12.15-13)*

5.1. Update ongoing testing

A short update was given on the various testings that are ongoing:

- PtO2:
    - Ames assay showed notable increases with two strains (TA98 +S9 and T100 +S9), but these were not considered a true compound related effect (attibutable

to a single eleveated replicate plate count + no confirmation in experiment 2). As such, absence of mutagenic activity was concluded.
- in vivo skin sensitisation testing scheduled and reporting expected soon.

- Platinum dinitrate:
  - The DRF in-life phase has been completed (to be followed by OECD407-421 assays). The dosing regime was 300-1000-3000 ppm in diet. At none of the dosing levels, effects were observed up to TD11. Therefore, it was decided to increase some dosing levels (300 -> 10000 ppm, 1000->7000 ppm) and continue the DRF for another 14d. All test animals were terminated as scheduled. Slight BW effects were observed for the high dose animals (10000 ppm). Test item stability (FT-IR), and diet concentration/homogeneity analysis is pending, as the study is put on hold till there is clarity on substance ID (cfr next paragraph). If substance sameness between Pt nitrate solid vs solution is confirmed, the study will continue.

5.2. Pt genetox: Status + way-forward substance ID Pt nitrate

The public consultations (PC) for testing proposals of 3 groups have been finalised. The one for HHPA-2AE is opened 4 October (runs till 19/11/18). Only the one for Pt dinitrate is pending.

For HHPA-2AE, ECHA contacted the lead registrant (LR) for clarification on substance ID. A clarification document has been included in the LR registration dossier and resubmitted. As the PC is open, the clarification is assumed to be accepted by ECHA. Pending action for this group is the drafting of a read-across justification report (RAJR). This is currently being drafted by the PMC secretariat. Some additional ^{195}Pt NMR analytics are being performed to confirm dissociation to the same toxicologically active species. The draft version will be send to the TE for input/review when ready.

For platinum dinitrate, ECHA contacted the lead registrant (LR) for clarification on substance ID. During a tox expert conference call, it was agreed to perform some additional analytics (^{195}Pt NMR, and EXAFS/XANES if required), investigate elemental composition and clarify/develop a manufacturing process+reaction scheme. The samples for Pt NMR analytics should be send ASAP by the registrants to the testing lab. The LR has send a solid and solution sample to the University of Karlsruhe for a preliminary EXAFS/XANES analysis. The outcome of this analysis will allow the institute to develop an offer for detailed analytics (if we need this). The Elemental analysis is under investigation by the LR, and the manufacturing process/reaction scheme will be developed with company volunteers once clarity on SID is obtained.

Regarding the further in vivo mutagenicity testing, the current best estimate that we might receive a final decision from ECHA is Q2-3 2019. Most likely, final decisions will arrive in groups, with those where the PCs have been finalised arriving first, and Pt dinitrate last (cfr. ongoing SID investigations). EPMF secretariat has informed with testing labs on availability to perform the proposed combined Comet/MN assay and the availability of historical control data for liver, stomach, duodenum and kidney. Covance, LPT and Envigo are considered potential candidate labs. Citox (outsource these studies) and Eurofins (no historical control data for kidney) not. The participants have good experience with Covance and LPT (noting the single bad experience with Covance for TCA), no experience with Eurofins. EPMF Secretariat will inform with these labs for an price estimate + experience with metals. The companies will check internally for good/bad experience with these labs and inform the

secretariat about their preference. The companies can also still suggest potential other labs to contact.

5.3. Karstedt Concentrate SID

ECHA contacted the LR of Karstedt Concentrate for clarification on substance ID. A clarification document has been included in the LR registration dossier, and ECHA has informally accepted. The only pending request is a change of substance identifiers to clarify that the substance containes also other constituents like the starting silane (next to the complexes), and that Pt is present as Pt(0). The current name is ‚Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes' and the proposed name by ECHA is ‚*1,3-diethenyl-1,1,3,3-tetramethyldisiloxane and its platinum(0) complexes*'. **The participants agree with this new naming.** Formal objections need to be mentioned to the PMC secretariat before 21 October 2018 COB. If no objections are received, the LR will update the dossier as mentioned in slide 69, and resubmit before end October 2018 as agreed with ECHA.

A ballpark estimate for an EOGRTS assay (basic design) gives a cost estimate of approx 535K euro, and the requirement for 7kg test item, confirming that the budget of 800K euro (as included in the 2019 budget) is realistic.

[*Post meeting note: the Karstedt Concentrate SID card will be updated to clarify the calculation method of the substance composition, as included in the registration dossier*]

Lunch break *(13-14)*

6. Rhodium and compounds *(14-14.45)*

6.1. Update ongoing testing

A short update was given on the various testings that are ongoing:

- Rh2O3:
  - acute tox (oral), skin irrit/corr and eye irrit/corr assays are scheduled for Sept-Oct 2018.
  - in vivo skin sensitisation testing scheduled and reporting expected soon.
  - oxidising properties being tested and shown to act as strong oxidizer. There is a chance that a classification as oxidizing solid is required. This will be communicated to the membership once confirmed.

6.2. Rh(III) genetox: status & further actions

The AMES assays for the 3 poorly water soluble Rh(III) compounds Rh2O3, Rh(OH)3 and Rh tris(2-ethylhexanoate) are finalised, and show no mutagenic potential. This confirms the EPMF hypothesis of absence of mutagenic potential for poorly water soluble Rh(III) compounds in comparison to the (moderately) water soluble Rh(III) cmpds.

The testing proposal for in vivo mutagenicity testing has been drafted by Bibra and reviewed by the EPMF secretariat. A RAJR for water soluble Rh(III) cmpds is currently being drafted by the EPMF secretatial. **The participants agree to send both documents to Mark Raffray for input/review, and in a second step to the EPMF members for input/review**.

The participant also agree that the solubility of RhI3 in water vs DMSO needs urgent investigation. The approach on slide 80 is considered OK. Spectral analysis/speciation is not considered to be required. The companies are requested to check if they can do the work (ie, dissolution of RhI3 in various water:DMSO mixtures and determination of soluble Rh(III) concentration by ICP-OES/MS) in house. If not, the participants agree that this work can be outsourced to an external testing lab.

7. Ruthenium and compounds (14.45-15)

7.1. Update ongoing testing

A short update was given on the various testings that are ongoing:

- RuO2:
  - skin irrit/corr: the substance is shown to be not irritant.
  - in vivo skin sensitisation testing scheduled and reporting expected soon.
  - Ames assay showed absence of mutagenic activity

8. Workplan and budget *(15-15.30)*

The 2019 budget has been presented. No remarks were made by the participants. As will be shown in section 9.1, the budget for Pd cmpds, Rh(III) cmpds, Rh cmpds (other) and Ru cmpds will slightly increase for TD work in 2019.

9. AOB, next meeting(s) and closing remarks *(15.30 -15.45)*

9.1. Organic Metal Salts vs Organometallics

During the EM EHS Autumn week, there was a presentation dedicated to the treatment of organic metal salts (OMS; metal + organic moiety) vs organometals (OM; metal covalently bound to C). For regulatory purposes, OMS (incl coordination complexes where metal has covalent-character bonds with O/N/S/P belonging to organis moiety) are considered as OM, and has to be assessed as such. Unless you can experimentally show rapid dissociation of the metal + organic moiety, and the organic moiety does not contribute (significantly) to the toxic effects. For metals, the latter means in most cases that, if rapid dissociation can be shown, the ‚generic' metals approach of ‚dissolved metal ions driving toxicity' applies. If not, a separate environmental assessment of the compound under consideration (separately or as a group if read-across is possible) is required. Rapid dissociation can be shown via Transformation/Dissolution testing (TD screening test, 24h; OECD TG29). EPMF has 11 substances in scope that might be impacted by this issue (cfr overview slide 95). The proposal is to test the more water soluble substances (ie, substances with water solubility >100 mg/L)

-Palladium acetate

-Dicarbonyl(pentane-2,4-dionato-O,O') rhodium and Di-μ-chloro-bis(hapto-1,5-cyclooctadiene) dirhodium(I)

-Rhodium (III) acetate

-Ruthenium acetate.

Besides these, we propose to also include those substances that have a chance to show rapid dissolution:

-Rhodium tris(2-ethylhexanoate)

and one of the Pd and Rh triphenylphosphine compounds:

- Dichlorobis(triphenylphosphine)palladium or Tetrakis(triphenylphosphine)palladium
- Carbonyl(pentane-2,4-dionato-O,O')(triphenylphosphine)rhodium, Carbonylhydrotris(triphenylphosphine)rhodium or Tris(triphenylphosphine) rhodium (I) chloride

The associated budget estimate (to be added to the 2019 budget of the relevant platforms for dossier maintenance) is (5500 euro per test):

-Pd cmpds: 11000 euro
-Rh(III) cmpds: 11000 euro
-Rh cmpds (other): 16500 euro
-Ru cmpds: 5500 euro

The participants agreed to review the above proposal internally and provide input/approval before 21 October 2018 COB. The budget will be added to the 2019 budget for the platforms affected.

9.2. Nanos

ECHA, EU COMM and OECD keep their activities regarding nanomaterials and their characterisation/assessment high. ECHA announced in their Newsletter that companies will be obliged to be compliant with the REACH requirements for nanomaterials by January 2020. Companies are requested to inform the EPMF Secretariat ASAP, and by the latest end 2018, in case they put nanoPGMs on the market that need registration under REACH. Afterwards, the EPMF Secretariat cannot commit to do all what's within its possibilities to have a nano registration dossier (as part of the bulk form) ready by January 2019. If registration is required, and testing needs to be performed, the reserves will likely need to be used as the 2019 budget will be fixed by that time. **The companies agree with the urgency and the proposal.**

* * *

ANNEX – Participants

Roland BRASCH, Heraeus (Germany)
Arno BUTHE, Heraeus (Germany)
Eliot DEAG, Johnson Matthey (United-Kingdom)
Maxime ELIAT, consultant for EPMF (Arche, Belgium)
Herbert FUCHS, Heraeus (Germany)
Rikki GORDON, Johnson Matthey (United-Kingdom)
Michael HUBER, C. Hafner (Germany)
Hitoshi KOSAI, Tanaka (Japan) (PM only)
Simona LAI, Varinor (Switzerland) (AM only)
Marie-Laure LEDRICH, Traxys (Luxembourg)
Olga LEMKE, BASF (Germany) – via conference call
Jelle MERTENS, EPMF (Belgium)
Michael THIEL, BASF (Germany)
Paul YLIOJA, Johnson Matthey (United-Kingdom)

Apologies
Sylvaine DUARRI D'HAENE, Umicore (Belgium)
Alexandra LEVESQUE, PX Group (Switzerland)
Hege STUBBERUD, Glencore Nikkelverk (Norway)
Steven VERBERCKMOES, Umicore (Belgium)