PGM Tox Experts and Work group

Minutes, Webinar, 31 March 2020 (14:00 – 16:00)

Chair: Michael Thiel (BASF, Germany)

Co-chair: Arno Buthe (Heraeus, Germany)

ACTION	WHO?	WHEN?
RhI3 dissolution with increasing DMSO concentrations – identify + contract CRO	EPMF	2020
Finalisation Pd PNEC review + read-across justification documents	EPMF	Q2-3 2020
Review Pdacac DNEL and risk assessment	EPMF/Bibra	Q2-3 2020
Check Pdacac dossier for presence of read-across to other Pd substances	EPMF	Q2 2020
Corn oil can be used as vehicle for PtN in vivo muta testing - communicate to CRO	EPMF	Asap
Monitor potential delays CRO experimental work due to Covid-19	EPMF	During period of Covid-19 restriction
Contract Paul Fowler for tris(nitrato-O)nitrosylruthenium mutagenicity advice	EPMF	April 2020
Provide names of mutagenicity experts to EPMF secretariat	Companies	Q2 2020
Classify Pd acetate as skin sensit 1 (H317)	Companies	asap
Contract CROs for further testing as indicated on slides 18 and 35	EPMF	April 2020

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

1.1. Reminder on Confidentiality and Competition Law
1.2. Tour de table and apologies
1.3. Approval of the agenda
1.4. Approval of the minutes of the last meeting (9 October 2019) and status of action points

Michael Thiel welcomed the participants reminding the anti-trust and competition law guidelines.

Exceptionally this meeting was held via webinar formal due to the COVID-19 restrictions.

The meeting started by a tour-de-table (see list of participants in annex).

The agenda of the meeting was approved.

The status of the action points of the autumn BtB meeting in October 2019 was summarized. The dissolution of RhI3 with increasing DMSO concentrations has not been investigated and will be kept in the action points list (to be performed later in 2020). The revision of the Pd PNEC and read-across justification document has been delayed due to the ongoing testing with Pdacac (acute fish toxicity assay) and the finalisation of the document on counter-ion contribution to the observed effects (document being developed under Eurometaux umbrella, being reviewed by ECHA and now under revision). This work will be finalised Q2-3 2020).

The draft minutes of the autumn BtB meeting (9 October 2019) were approved.

2. Update ongoing and future testing

2.1. RDT/Reprotox assays Pdacac

The status of the finalised RDT/Reprotox assay with Pdacac was summarised. The in-life phase of the full OECD422 assay was finalised mid May 2019. A draft report was available in November 2019 and commented by the members. Threshold concentrations for systemic/developmental/repro tox vary between NOAELs 3 - 30 mg Pdacac/kg bw/day. No change in C&L triggered. In the current Pdacac dossier, $Pd(OH)_2$ is used as read-across substance (NOAEL 1000 mg/kg/d). The new NOAEL is significantly lower and will trigger a review of the risk assessment in the Pdacac dossier. Bibra has been contracted to revise the DNEL and will work on this in March-April 2020. The risk assessment will also be reviewed and might trigger more stringent risk management measures (RMM) to ensure safe use.

The dataset of Pdacac will be checked if read-across to other palladium substances is still included in other parts of the dossier.

2.2. DRF assays PdCl2, Na2PdCl4 & PtN

The status of the finalised DRF assays with $PdCl_2$ and Na_2PdCl_4 were summarised:

- $PdCl_2$: an uncommon palatability effect was observed in the first dose range finding (DRF) study using dietary administration. Therefore, it was agreed to perform a second DRF using gavage administration and a lower dosing regime. The second DRF started at 0 – 30 – 100 – 300 mg/kg/d but the top dose had to be lowered to 200 mg/kg/d due to loss of BW. There was one male HD animal sacrificed at day 5. All other test animals survived till test day 14. No pathological changes or effect on organ weights at termination. Suggested dosing for further testing (by the CRO that performed the test) is 0 – 30 – 100 – 200 mg

$PdCl_2$/kg/d. This dosing level, as well as the test setup to be used, will be discussed once the new CRO has been contracted (see discussion on LPT).

- Na_2PdCl_4: The DRF has been finalised and did not show major effect on males/females up to the high dose (10000 ppm test item in diet). Suggested dosing for further testing (by the CRO that performed the test) is 0 – 1000 – 3000 – 10000 ppm. This dosing level, as well as the test setup to be used, will be discussed once the new CRO has been contracted (see discussion on LPT).
- PtN: The DRF has been finalised after an extension with 14 days (28 days in total) and increase in dosing regime from 0 – 300 – 1000 – 3000 ppm to 0 – 10000 – 7000 – 3000 ppm. No major test item related effects at any dosing level. Suggested dosing for further testing (by the CRO that performed the test) is 0 – 3000 – 7000 – 10000 ppm. This dosing level, as well as the test setup to be used, will be discussed once the new CRO has been contracted (see discussion on LPT).

2.3. LPT & animal welfare concerns

On the 23rd of October 2019 EPMF was made aware of animal welfare concerns at LPT. An overview was given of the actions that were taken (after discussions with the membership). In summary:

- 24th Oct: All scheduled/ordered in vivo work put on hold except the DRF with $PdCl_2$ that started a few days earlier.
- 29th Oct: Formal letter to LPT, with reply from LPT the same day
- 18th December: Site visit scheduled but cancelled by LPT on the 12th due to GLP inspection by local German authorities.
- 13th February: GLP inspection report received from LPT

At this moment all in vivo testing at LPT is either finalised or hasn't been initiated yet and is put on hold.

The way forward (as approved by the EPMF membership and Board):

- The tests that were put on hold will be assigned to an alternative CRO and a formal letter to terminate the studies that were put on hold earlier, will be issued.
- LPT will be requested to finalise the remaining reports asap and send the remaining test item to the refiner/alternative CRO.
- LPT will not be considered for further in vivo testing unless decision is annulled in the future.

Additional costs that might associated with this decision have been foreseen in 2021 draft budget.

2.4. Status update on the Pt in vivo mutagenicity testing

An overview was given on the status of the 5 in vivo mutagenicity tests placed at Charles River Laboratories ('CRL'; Den Bosch, NL)

HHPA-2AE:

- Development and validation of an analytical method for dosing formulation completed on the 22nd of March 2020. Unaudited draft report expected 19th April 2020. Corn oil was used as vehicle.
- The combined Micronucleus and Alkaline Comet Test started on the 10th of February 2020. The animals were dosed at 500, 1000 & 2000 mg/kg. TK timepoints at 1, 3, 6, 12 and 24h. Experimental phase finished, slides are currently being analysed. Availability of results on the 1st of April 2020.

Tetraammineplatinum dichloride:

- Development and validation of an analytical method for dosing formulation started on the 17nd of March 2020. Unaudited draft report expected 17th May 2020. Corn oil was used as vehicle
- The combined Micronucleus and Alkaline Comet Test started on the 9th of March 2020. TK timepoints at 1, 3, 6, 12 and 24h. Main study will be performed in male animals only at top dose of 1000 mg/kg. Availability of results on the 1st of May 2020, proposed draft report date 28th of June 2020.

Diammonium hexachloroplatinate:

- Development and validation of an analytical method for dosing formulation will start on the 12th of April 2020. Unaudited draft report expected 10th May 2020. Corn oil was used as vehicle
- The combined Micronucleus and Alkaline Comet Test will start on the 4th of May 2020, proposed draft report date 23rd of August 2020.

Dipotassium tetrachloroplatinate:

- Development and validation of an analytical method for dosing formulation started on the 23nd of March 2020. Unaudited draft report expected 24th May 2020. Corn oil was used as vehicle
- The combined Micronucleus and Alkaline Comet Test started on the 16th of March 2020. TK timepoints at 1, 3, 6, 12 and 24h. Main study will be performed in male animals only at top dose of 100 mg/kg. Availability of results on the 1st of May 2020, proposed draft report date 28th of June 2020.
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PtN:

- ECHA hasn't evaluated the TP yet
- Test substance delivered 26th of February
- The participants agree to use corn oil as vehicle.

Except for unforeseen delays, all test results should be available in time to allow dossier update and submission before the deadlines set by ECHA. Last week Friday (27 March 2020), CRL confirmed via phone that all EPMF experimental word was proceeding as scheduled. This situation will closely be followed-up by EPMF secretariat.

2.5. RhCl3 hydrate upgrade to Annex VIII

Upon request from an EPMF member company, the REACh dossier of rhodium trichloride will be updated from Annex VII to VIII (10-100 ton/yr). Datagap analysis has been performed. After discussion with the PGM Tox Experts:

- A RDT/Repro screening assay (in line with OECD 407/421) will be performed.

- to fill the data gap for skin sensitisation, an in vitro skin corrosion test will be performed to clarify the existing inconsistency between substance pH, the existing negative in vivo skin irrit/corr study and existing positive in vivo eye irrit/corr study. The substance hydration status and acid reserve are under investigation as possible explanation. If that doesn't provide an answer to the inconsistency, the in vitro skin irrit/corr will be performed. If this confirms skin irrit/corr potential, then skin sensitisation testing will

be waived. If this does not confirm skin irrit/corr potential, then skin sensitisation testing will be considered.

- additional testing for oxidising properties, toxicity to algae and toxicity to micro-organisms will be organised.

2.6. Genotoxicity Tris(nitrato-O)nitrosylruthenium

Tris(nitrato-O)nitrosylruthenium was selected for an update from Annex III to regular Annex VII dossier. Clear evidence of mutagenic activity was detected in the AMES assay, and a TSCA notification has been drafted. The follow up in vitro HLM assay confirmed the mutagenic activity, and the FISH analysis showed a predominant clastogenic mode of action. A TSCA notification has been drafted. The positive in vitro test data trigger further investigation and expert advice is needed.

Prof Kirkland was contacted. He confirmed he'll stay available for the Pt work but denied the Ru work due to his plan to reduce his workload. Prof Kirkland suggested Paul Fowler as alternative expert. He has worked together with Paul Fowler in the past and recommended him for his vast experience in the field. Eliot Deag worked with Paul Fowler before and confirmed his genotoxic expertise. The participants agree to contract Paul Fowler for this project. We should ensure to instruct Paul Fowler about basic PGM chemistry (like we did with Prof Kirkland in the past), but this learning should be part of the very conservative estimate of 5 working days he provided to us. As Prof Kirkland will reduce his workload over time, we should start thinking of further alternative experts (ideally with (precious) metals experience). The participants are requested to provide the EMPF secretariat suggestions for alternative muta experts.

2.7. Other testing

Pd acetate showed a positive response in an in vivo LLNA (OECD 429) study and needs to be classified as skin sens cat 1. A TSCA notification is under preparation

Pd ecotox review is still ongoing as two pieces of information are still lacking:

- The "counter-ion" contribution to observed effects document which is needed for the RA justification has recently been sent back by ECHA and comments need to be reviewed by the authors now
- Pdacac acute fish tox test had to be repeated and is just finalised (LC50 = 5.5 µg/L)

The results of the other tests have been reported in the slides and do not require special attention.

2.8. Future testing

Two types of future testing are required. First the in vivo tests originally contracted at LPT (but put on hold due to animal welfare concerns) have to be reassigned to another CRO. CRL is the recommended CRO by the EPMF secretariat and PGM WG chairs. The participants to the meeting have full confidence in CRL and agree with the proposal.

For the 2020 testing program (approved during the 2019 BtB meetings), testing has to be performed for the upgrade of the $RhCl_3$ hydrate dossier and to strengthen/investigate the RA for $Pd(OH)_2$, RuO_2 and PtO_2. For phys-chem, genotox and ecotox testing, BAM, DMT, Covance and Fraunhofer are the proposed CROs (cfr. slide 35). In addition, ICCR is proposed for the acute tox endpoints, to investigate if they could be a good

option for future testing since several of other CROs are not recommendable anymore due to bad experiences (e.g. LPT & Covance) or no longer available as independent CRO (e;g. acquisition Citox by CRL). The participants agree with the proposed CROs.

3. IPA – Update main activities

Eliot Deag presented the slides prepared by Mark Hosford (IPA). In short:

-the announcement of the name change of the Science Task Force (STF) to Health and Environment Science Committee (HESCom).

-ACGIH has put Pt on the 'Under Study'-list. The reasons for listing are unknown but could lead to a change in TLV.

-HESCom is currently working on several projects which were briefly explained:

-An extension of the epidemiology study to include data up to 2016 – once published (March 2019 but potentially delayed), this will strengthen the dataset and might potentially re-initiate regulatory appetite to review the Pt OEL

-The quantification of skin exposure (as relevant parameter to induce Platinum Salt Sensitisation), and the assessment of PGM skin penetration using an in vitro assay (building further on earlier publication).

-PGM genotoxicity: developing a communication strategy around the EPMF in vivo muta testing and to investigate the genotoxicity potential of Pt nanoparticles.

-Real-time monitoring of workplace Pt exposure

It was concluded that this exchange was useful and should be continued in the future as we can learn from each other and the results from each other's work could improve the overall knowledge on the PGMs.

4. Draft budget 2021

The 2021 draft budget has been presented. No remarks have been made by the participants.

5. AOB, next meeting(s) and closing remarks

No any other business was raised.

A decision on the GA meeting (scheduled for 3-4 June 2020) will be communicated soon to the membership. Next EPMF BtB meetings are scheduled 6-7 October 2020 in Brussels. Date (timing)/place will be confirmed in due time.

Annex 1: Participants

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