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14 OCTOBER 2015, 09:00 – 12:00 CET
METALS CONFERENCE CENTRE – ALUMINIUM ROOM
RUE DU DUC 100 – 1150 BRUSSELS (BELGIUM)

PGM Tox Experts Meeting – Minutes

1 Welcome and Introduction

1.1 Reminder on Confidentiality and Competition Law

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

1.2 Tour de table and apologies

The list of participants is available in Annex 1.

1.3 Approval of the agenda

The agenda is available in Annex 2. No remarks / additions; the agenda was approved.

1.4 Approval of the minutes of last meeting, status of action points

No remarks / additions were made on the minutes from the last meeting; the minutes were therefore approved.
A table with the status of the action points from the last meeting is available on slides 5-7 in Annex 3.

The action point on ABUK has been completed: bibra reviewed the Ames assay and considers it robust. The pre-incubation method is considered to provide more suitable conditions for evaluating the mutagenic potential of these compounds, over the standard plate-incorporation Ames protocol. The methodology results in a transient, acute exposure of the bacteria during the pre-incubation step; the exposure is substantially reduced upon incorporation of the bacteria onto the plate. Bacteria in the plate incorporation procedure, on the other hand, are exposed to a continuous dose of the test agent, and this may result in exceedingly high toxicity, preventing the expression of mutagenicity.

The recent Ames study on Palladium (II) di[4-oxopent-2-en-2-oate] (Covance study no. 8284204, October 2013) included an additional pre-incubation step, thus appropriate for this type of substance.

Additionally, a new in vitro mutation assay at the hprt locus of mouse lymphoma L5178Y cells (MLA) has been conducted (Covance study no. 8284304, June 2014) and this was also negative.

No additional testing for mutagenicity is considered necessary.

All other action points are either completed or are on the agenda for discussion at this meeting.

2 Substance identification and sameness of PGMs - update

2.1 General approach substance sameness (KR)

The PGM tox experts group agreed with the principle that the decision on sameness is the responsibility of each individual registrant.

PMC pointed out that for substances that exist only in solution, care should be exercised when calculating the tonnages. In these cases, a minimum percentage of water/solvent has to be defined below which the substance is not stable any more. A precedent established for Perrhenic acid

(discussion with ECHA) indicates that this amount should be reported as an 'impurity' and contributes to the tonnage of the respective substance.

The proposed timeline of circulating SID cards in Q4 was agreed.

PMC reminded the group to provide the relevant spectra, if they haven't done so yet. PMC can only finalize and circulate the SID cards when the spectral information and CoAs have been received.

The PGM tox experts group suggested to also agree a timeline for circulating the SID cards to the SIEF[1].

2.2 Changes in substance ID (KR)

An update was provided on recent changes in substance ID recommended by the sameness experts group (slides 12-13). No questions or objections were raised

2.3 Karstedt concentrate (KR)

An update was provided on the status of the work on Karstedt Concentrate. PMC is proceeding with the planned testing programme. The cooperation with Reconsile proceeds slowly and is difficult. PMC members have completed the analytical work regarding substance ID; no feedback has been received from the Reconsile members at the time of the meeting. The University of Bristol (which conducted the NMR work) indicated that only 2 Reconsile members have provided test material.

The substance identification of Karstedt Concentrate is difficult since the reference paper on NMR is wrong and expert judgment will need to be applied when interpreting the results. DB indicated that some Pt195 NMRs show Pt-Cl peaks (which may be indicative of the presence of toxicologically significant chloro- species).

Action: DB to discuss status with Bristol U, and report back to expert group on potential implications on sameness/ SID

2.4 PGM nano forms (KR)

PMC presented the status of the nano characterization programme. The programme is proceeding slower than planned, mainly due to confidentiality issues. The results of the coordinated characterization exercise have been reported, however the results of some tests could not be made available to PMC since no permission from the data owner has been granted (post meeting note: permission granted in the meantime, data are available to PMC now). Furthermore, two companies have been conducting the evaluation internally and the results from one company were not finalized yet.

The expert group concluded that it is not possible to have a meaningful discussion of potential next steps at that stage. It was recommended to revisit the discussion once all data is on the table.

Action: PMC to reconvene expert group once all data is available

[1] post meeting note: ongoing within PMC

3 PGM testing programme

3.1 PGM ecotoxicity testing (all)

Karstedt Concentrate: before the main hydrolysis test can commence a preliminary test is required as method development. Very little information is available on potential degradation products and analytical methodology, making it too risky to start with main test already

The group recommends to read-across from rhodium trinitrate to diammonium sodium hexakis (nitrito-N) rhodate for the fish endpoint. This is a formal data gap for diammonium sodium hexakis (nitrito-N) rhodate, but acute toxicity to fish is not the driving ecotox effect for Rh (III) compounds since algae are significantly more sensitive. Therefore, conducting a fish test on that substance would not change the assessment and thus a fish test will not be necessary any more, and it was agreed to remove it from the testing program for this substance.

Action: WCA to draft waiver

Tetraammine compounds: Read across for chlorinated Pt- and chlorinated Pd- substances

A concern was raised that read across from chloro-containing substances may be overly conservative for these substances. The group recommended that tetraammine platinum dichloride should not be associated with Pt substances with chloride as a coordinated ligand. Tetraammines are structurally different and the chlorides are not directly coordinated in that case. Hence there is no rationale for data gap filling utilizing tetraammine PGM chlorides. Read across from existing ecotoxicity data on other tetraammine Pt/Pd salts was considered sufficient instead.

Action: PMC and WCA to confirm the workability of using other tetraammine Pt/Pd salts for the purpose of read-across

No dispersive/diffuse uses have been reported in the use questionnaires for tetraammine platinum dichloride, contrary to previous discussions. If there are no dispersive/diffuse uses then the substance can be exempted acc. Annex III of Reach and no ecotox tests will be required

Action: members to inform PMC Sec by end Oct if they have dispersive/diffuse uses for tetraammine platinum dichloride, e.g. for plating applications.

New data from the algae test on Tetraammonium decachloro-mu-oxodiruthenate have become available. PMC is currently reviewing if any changes to the classification will be required. The PGM WG will be informed if necessary

3.2 PGM genotoxicity testing (all)

3.2.1 Rh (III) genotoxicity

Testing on Tetraammonium decachloro-mu-oxodiruthenate and Rh (NO3)3 (Ames assay of Rh (NO3)3-solution) is currently ongoing. Testing on Karstedt Concentrate is currently on hold. All other tests have been completed

3.3 Sensitization/ Irritation (all)

3.3.1 Karstedt Concentrate sensitization

New existing studies from Reconsile have become available. The studies are property of Reconsile and confidential, so no details could be shared. Bibra have reviewed the studies on a confidential basis; a summary is provided in slide 47.

Five Reconsile studies are available on the dermal sensitisation endpoint for Karstedt Concentrate

- Bibra consider all studies to be reliable
- Study results are inconsistent but generally do indicate sensitisation potential in the guinea pig assays. A human HRIPT was negative.
- Not all report details (e.g., appendices) have been provided to PMC by Reconsile. Also, no information on test item purity is available. This leaves knowledge gaps particularly in respect of test article characteristics. Hence the current state of knowledge precludes interpretation of the sensitisation assays at this time.

Due to the possible use of immunogenic chloroplatinates, such as CPA, as precursors in the synthesis of KC, the group recommended that as a first step, we need to be sure about the substance characteristics, synthetic route, and purity. As a proxy, the residual Cl-content (e.g., measured via ICP) of any reference substance should be checked to see if chlorinated platinum compounds are included as impurity.

Action: PMC to request respective CoAs from Reconsile.

Decision: all planned mamm. tox. studies for Karstedt Concentrate should be put on hold until this is clarified

The expert group also recommended PMC to challenge Reconsile on these studies:

- If results are real, i.e., positive for sensitization potential why were these classifications not previously officially notified to the Classification and Labelling Inventory ? [There is no classification for skin sensitization indicated in any of the seven Aggregated Notifications for “Platinum, 1,3-diethenyl-1,1,3,3-tetramethyldisiloxane complexes” detailed in the C&L Inventory – ECHA]. Also, why was no notification to US EPA made under TSCA 8(e)?
- If the results should turn out to be real, this could have significant impact on Karstedt Concentrate uses since many Karstedt Concentrate applications are subject to biocompatibility / minimal toxicity requirements.
- If the above information obtained from Reconsile is still inadequate, the option exists to conduct further testing (LLNA) for PMC reference KC substance(s), based on the justification that uncertainties affected the previous tests.

Action: PMC to discuss above points with Reconsile

3.3.2 Other

PMC informed the group that initial data from an LLNA tests on Tetraammonium decachloro-mu-oxodiruthenate indicate potential sensitizing effects. A TSCA 8(e) notification may be required.

3.3.3 HHPA-2AE irritation

A recent EpiDerm test (OECD 439) indicated that the substance should be classified Corrosive Skin Cat 1 or 2. This may be reportable data under TSCA 8(e) and notification may be required (probably as a FYI on the basis that many aminoethanol complexes are corrosive or irritant).

Next steps: the test approach as outline in slide 49 was approved: conduct an EpiSkin test (OECD 431) potentially followed by Corrositex, and rabbit eye (OECD 405) test if the latter is triggered. The costs are covered in current budget.

3.3.4 Karstedt Concentrate irritation

The group re-confirmed the above conclusion (under 3.3.1) for Karstedt Concentrate: all studies on irritation/ sensitization should be put on hold until the SID has been clarified

Action: PMC to check if EpiSkin test can be extended to discriminate between Cat. 1A/B/C[2]

3.4 PGM acute/repeated dose testing (all)

3.4.1 HHPA-2AE Testing Strategy

After reconsideration of the previously discussed RDT testing strategy, which envisaged an OECD 407 study with a nested MN segment, the expert group proposes a revised testing strategy:

- An OECD 422 study should be started immediately (which will address the identified reproductive toxicity and repeat dose toxicity data gaps).
- Submit a separate testing proposal (TP) for an in vivo MN (OECD 474)

Action: PMC to confirm approach with LR (no company representative present at the meeting)

The reason for reconsidering was that

- We need to be able to derive a DNEL at an earlier stage (TP will only be submitted together with final dossier)
- A reproductive toxicity data gap is now identified.
- A combined OECD 422and in vivo MN study would actually combine 3 separate studies, with potentially conflicting design parameters. The revised study plan (as set out above) will make this practically easier to manage and increase likelihood of success.

3.4.2 RuCl3 testing strategy

Additional data have become available on 'Ruthenium acetate'; hexakis(mu-(acetato-O:O'))-mu3-oxo-triangulo-triruthenium acetate; CAS Number: 55466-76-7. The study is owned by third party and could not be circulated to the PGM WG. A review by an independent consultant (Mark Raffray) was conducted.

The conclusions of review were :

[2] Post meeting note: done. Under the most recent OECD TG431 (adopted 28 July 2015) a partial sub-categorisation of corrosion is possible with EpiSkin to 1A or 1B/C. It does not allow discrimination between sub-category 1B and sub-category 1C.

- Study considered not useful for our purposes, and in particular for read-across to RuCl3 / Ru(3+) compounds.
- Recommendation to perform separate OECD 407 and 421 studies
- Consider inclusion of a satellite (recovery) group in any newly commissioned TG 407 in order that the reversibility of any changes in the spleen can be evaluated.

A verbal discussion of Mark Raffray's review and recommendations took place. The group endorsed the above conclusions by Mark as they related to closure of the repeat dose toxicity data gap for RuCl3:

- Similar to the other RDT studies, and based on confirmatory advice from RSA, there will be a need to extend the preliminary study (DRF) to at least 2 weeks duration
- A discussion on the best route of exposure indicated that of the available options, dietary exposure will be the preferred option in this case. This avoids potential complications with re-speciation of RuCl3 in buffering vehicle media.

Action: PMC to circulate papers on RuCl3 speciation: M 14 July, forward to Niss, Buthe, Dave

3.4.3 Diammonium hexachloroplatinate

An action point from the previous meeting was to review if a classification for reprotoxicity will be required based on the results from the recent OECD 421 study. Bibra reviewed the data and concluded that no classification will be required. The group endorsed the conclusion

3.5 PGM nanomaterials – impact on ITS (all)

As discussed under agenda point (2.4) the group considered it premature to discuss this in detail at this stage. No further discussion took place

4. Project Planning

4.1 Time line (KR)

DN(M)EL derivation for Chloroplatinates based on respiratory sensitisation
PMC informed the group that it is proposed to contract an external expert for this point. Given the importance of this endpoint a careful consideration of the options for the DN(M)EL derivation and technical methodologies will be necessary

- There was general agreement to contract an external expert
- The group also indicated that they are interested in following this process closely. It recommends to the PGM WG to set up a dedicated steering group for this project

Action: members to indicate to PMC their representatives for the steering group as soon as possible
Action: PMC to recirculate RfP to the group

4.2 New study requirements (KR)

This agenda point has already been covered by the discussions on the previous agenda points.

5. AOB, next meetings/calls and closing remarks

The next PGM WG meetings will be held 19-20 April 2016 and 5-6 October 2016 at the Metals Conference Centre in Brussels.

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