PGM Tox Experts meeting

Minutes, Conference call 27 February 2020 (14-15 CET)

Participants: Arno Buthe and Herbert Fuchs (Heraeus), Nissanka Rajapakse and Eliot Deag (JM), Olga Lemke (BASF), Steven Verberckmoes (Umicore), Maxime Eliat and Jelle Mertens (EPMF)

Slides were circulated ahead of the meeting, and were the basis for the below summarised discussion.

1 Genotoxicity Tris(nitrato-O)nitrosylruthenium: way-forward

Jelle summarized the findings of the in vitro genotoxicity assays (AMES and in vitro HLM) performed with this substance. Both assays confirmed a mutagenic potential of the test item, and a predominant clastogenic mode-of-action was shown in the FISH analysis.

The participants agree to not yet classify this substance for mutagenicity, since:

- the current observations of a potential mutagenic potential are only based on in vitro assays, and
- a follow-up testing (in vivo genotoxicity) will be considered immediately.

This decision to not yet classify is in line with earlier (comparable) cases within the EPMF (e.g. PMCN and Pt compounds), and with ECHA guidance.

The participants agree to contact Prof Kirkland for an assessment of the test data and give his advice if and what further in vivo testing would be best to answer the concern identified in the in vitro assays. The data for the test item can be provided to prof Kirkland, as well as the genotoxicity data for other Rh(III) compounds (RuCl3 and Ru acetate). The participants are unclear about the speciation of Ru(III) vs Ru(IV) compounds in the GI tract. Therefore, if not speciating to similar species, care needs to be taken to not over-group. Therefore, the chemistry of Ru(III) vs Ru(IV) should be investigated first. Only if expected to be similar, then the Ru(IV) data should be provided to prof Kirkland.

Olga will also send a link to an ECHA document which provides guidance on the in vivo assays that should be used when different sets of in vitro test data are available

***[Post meeting note**: in the PGM SID clarification documents of Dave Boyd, the following is written: 'All of the PMC substances fall into this category of mixed chloro-aqua complexes, except Palladium(II) dichloride, Rhodium(III) triiodide and Tetraammonium decachloro-mu-oxodiruthenate(IV)… The Tetraammonium decachloro-muoxodiruthenate(IV) is created by the fusion of two Pentachloroaqua ruthenium (IV) species with an oxo bridge replacing the two aqua ligands.' On this basis, I propose to only provide the Ru(III) test data to Prof Kirkland, because of an expected different chemistry.]*

Actions:

-do not classify Tris(nitrato-O)nitrosylruthenium based on in vitro data only

-request expert advice of Prof Kirkland for further in vivo testing, and provide him the genotoxicity data for other Ru(III) test items. - ***ongoing***

-investigate Ru(III) vs Ru(IV) chemistry, and provide Ru(IV) genotoxicity data to prof Kirkland if speciation is similar – ***cfr. post-meeting note: only Ru(III) data will be provided because of different chemistry, unless the companies are of a different opinion***

-Olga to provide link to ECHA document - ***done***

2 Irritation/corrosion potential RhCl3 hydrate

Maxime summarised the intuitively inconsistent findings regarding irritation potential of the substance and the pH of the substance:

-negative in vivo skin irritation/corrosion data – Mayr 1986

-positive in vivo eye irritation/corrosion data (classified as Eye Dam 1) – Mayr 1986

-pH = -0.53

The observations might be related to a different hydration status of the substance (affecting solubility) as well as the acid reserve (and thus the potential to be rapidly neutralised when administered topically). The Mayr 1986 studies should be checked for SID information (purity, water solubility, acid reserve…). The participants agree to run an additional in vitro skin irritation/corrosion assay to check the negative in vivo finding. The test item needs to be carefully selected to avoid excessive HCl impurities, and the buffering capacity should be known.

Once the in vitro test data are known, a decision can be taken on the way forward with datagap filling for skin sensitisation (waiving based on corrosion vs testing).

It was mentioned that some acute toxicity has been observed with RhCl3 hydrate, so that OECD407/421 assays in a sequential testing would be recommendable.

[Post meeting note: The Mayr studies are company owned and can thus not be circulated. All Mayr studies were performed with the same substance $RhCl_3.xH_2O$ with a Rh content of 37 – 40% and purity of 99.5%. Dark red crystals. Soluble in water and ethanol. No mention of HCl or buffering capacity.]

Actions:

-check with companies on RhCl3 specifications - ***ongoing***

-run in vitro skin irritation/corrosion test

-use the in vitro test data as basis to re-consider skin irrit/corr classification and datagap filling for skin sensitisation

-the RDT/Repro screening can be done in an OECD407/421 sequential test setup.

3 Acute toxicity Pd(OH)2: waiving vs testing

Maxime explained that there is an OECD422 assay available for this substance showing no effect up to the limit dose (1000 mg/kg bw/d), which can be used as a basis to avoid acute toxicity testing. Bibra developed such argumentations before, and can do this within 2 days.

The participants are of the opinion that 2 days are excessive for writing this argumentation. It should be kept as short as possible, and can be largely based on the OECD422 DRF and full assay. The argumentation should

be developed as a weight-of-evidence, because a waiver has a high chance of being rejected (no standard waiver).

Testing for acute toxicity should be avoided as far as possible if no clear red flags are triggered by the substance properties.

Actions:

-develop WoE argumentation to waive the need for an acute toxicity test using the findings of the OECD422 DRF and full assay.