Karstedt Concentrate: Conference call PGM TE on OECD422

(31 March 2017, 11-11.15)

1. Participants list:

Michael Thiel (Chairman PGM WG) and Olga Duerr (BASF), Mark Raffray (Consultant), Steven Verberckmoes (Umicore), Nissanka Rajapakse and Mark Hosford (JM), Roland Brasch, Herbert Fuchs and Arno Buthe (Heraeus), Sandra Allen (RSA), Maxime Eliat and Jelle Mertens (PMC)

The below minutes reflect the main discussion points and agreements of the call, and need to be considered together with the documents and slides (kindly prepared by RSA and Mark Raffray) that have been presented and sent to all participants ahead of the call.

2. Summary of the call

Sandra received additional historical control data from LPT. There is an increased post-implantation loss observed in all treatment groups. The mean post implantation loss is outside the historical control range for the mid and high dose groups. This effect is considered being of concern by the participants, whereas the study report considers this as of 'no concern'. In the high dose group, 3 of 9 dams are outside the historical control range. In the mid dose group, the data are skewed due to a high post implantation loss for one dam [n° 56].

There is an inconsistency on pages 230 and 232 in the draft report regarding dam n° 58 (‚*animal not pregnant*' vs ‚*total implantation loss*'). This needs to be clarified, as it is important for deciding on NOAEL and classification. For the remainder of the discussions, participants assumed ‚*no pregnancy*' to be correct (as suggested in other tables).

ACTION POINTS:

- **RSA to clarify with LPT the inconsistency on pages 230 and 232**
- **LPT to update the study report according to PMC's interpretation (RSA to contact LPT)**

Mark R was asked by PMC Secretariat to review of the OECD422 study with the ligand (TMDS). There were similarities in the studies with TMDS and KC, but the implantation and post-natal stage effects were stronger with KC than with TMDS (recognizing that the former parameter was poorly reported in the TMDS study report). Hence drivers for classification are stronger in the case of KC. Whether the overlaps between the KC vs TMDS profiles is due to the ligand alone is difficult to judge without additional evidence (e.g. TK). When comparing the profiles of KC and TMDS to other cyclosiloxanes, some similarities are suggested, for instance with D4 (which is currently classified as Repr2). Despite these similarities, there are also clear differences in DART profile (e.g. in D4's impact on fertility whereas post-natal effects were absent).

A NOAEL of 125 mg/kg/d is proposed:

-in the high dose, multiple parameters are affected

-in the mid dose, only 1 parameter is of concern, and this effect is strongly driven by a single animal. Other effects in the mid dose group are considered marginal.

It is mentioned that there remains a risk that regulators will consider the low dose (30 mg/kg/d) more appropriate as NOAEL.

Considering the observations, the participants agree with the mid dose (125 mg/kg/d) as NOAEL.

ACTION POINTS:

- **BIBRA to draft the robust study summary, and PGM Tox Experts to review before inclusion in the dossier.**
- **BIBRA to derive DNELs based on a NOAEL of 125 mg/kg/d**

Sandra summarised the findings with respect to potential classification needs. The effects support a classification as Repr2 (pre- and post-natal reprotoxicity), but multiple effects might as well support Repr1B. Classification as Repr2 is supportable as:

-in the high dose animals, a minority was affected (3/9)

-in the mid dose animals, data are skewed by a single animal

-some siloxanes are classified as Repro2 and are not considered highly potent (cfr. limited assessment of Mark R)

Similar to the NOAEL, it is mentioned that there remains a risk that regulators will consider classification as Repr1B more appropriate.

If classified as Repr2 based on a screening study, follow-up testing is required according to ECHA Guidance (not needed if precautionary classification as Repr1B is chosen). An EOGRT (OECD443) with a basic study design is considered most appropriate (other assays like PNDT (OECD414) are not adequately covering the concerns like pup mortality or body weight loss).

The participants agree to classify KC as Repr2, and include in the registration dossier a TP for an EOGRT assay (OECD443) with basic study design.

There is no need to read across this classification to other (Pt) REACH dossiers: the effect is considered to be related to the Pt-siloxane complexes.

The data do not support an additional label for effects via lactation.

A TSCA 8(e) notification needs to be prepared.

ACTION POINTS:

- **PMC secretariat to inform SIEF (incl. Reconsile) about the above decision**
- **Update KC classification to Repr2 on PMC website once agreed by SIEF / Reconsile (+ communicate to IPA)**
- **PMC to prepare TSCA8(e) notification w/c 3 April**

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