Silver Tox Experts Call PMC / ESTF

Draft minutes, call 28 September 2018 (14:30 - 15:30 CET)

List of participants

PMC:			
1.	**Katrien Arijs**	Consultant for PMC	Belgium
2.	**Arno Buthe**	Heraeus	Germany
3.	**Rikki Gordon**	Johnson Matthey	United Kingdom
4.	**Marie-Laure Ledrich**	Consultant for Traxys	Luxembourg
5.	**Jelle Mertens**	PMC	Belgium
6.	**Nissanka Rajapakse**	Johnson Matthey	United Kingdom
7.	**Steven Verberckmoes**	Umicore	Belgium
ESTF:			
1.	**David Andrew**	Consultant for ESTF	United Kingdom
2.	**Andrew Goodyear**	Consultant for ESTF	United Kingdom
3.	**Germaine Truisi**	Thor	Germany
4.	**Ian Watt**	Dow	United Kingdom

Draft minutes

1 Welcome and Introduction

Participants were reminded that the meeting is confidential, and that the terms of the non-disclosure agreement signed in December 2013 by PMC and ESTF apply.

2 Background and brief update on respective regulatory processes

Cf. slides 3-6 in Annex 1:

- Slide 3 shows the overlap between the REACH registered Ag substances (PMC) and the Silver Containing Active substances (SCAS) registered under the BPR (ESTF). This illustrates that regulatory decisions have shared relevance for both sectors.
- Current situation **silver reprotox** (slide 4): The scientific data-gap related to reprotoxicity of Ag was addressed by PMC in 2015 by submitting a **testing proposal (TP) for an extended one-generation reproductive toxicity study (EOGRTS)** in the Ag metal REACH dossier. Since 2015, further research has been published regarding the reproductive toxicity potential of ionic Ag, extending the available dataset but still presenting non-definitive outcomes. Therefore, the TP was updated in April 2018. It is noted that, even if the TP is accepted, the outcome of the EOGRTS is highly unpredictable and the risk of classification of Ag as Repr cat. 1B still exists. It is further noted that this discussion is relevant for any substance generating ionic Ag, and thus the **outcome of the proposed EOGRTS has relevancy for PMC and ESTF**.
- The TP is now under evaluation by ECHA (cf. process on slide 5) and **PMC is still waiting for the Draft Decision (DD)** that should arrive in the coming weeks. The options for the DD are:
    a) Acceptance of the TP;
    b) Acceptance of the TP with modifications of the testing conditions;
    c) Acceptance or rejection of the TP but requiring one or more additional tests;

d) Rejection of the TP.

Taking into account the evaluation process / timeline, if the TP is approved, PMC does not expect to initiate the EOGRTS before summer 2019, with full outcome likely to be reported by 2021.

- KemI recently indicated to ESTF that they intend to prepare **CLH proposals for silver nitrate and elemental silver possibly including a Repr cat 1B classification** (cf. slide 6). The timeline for these CLH proposals is currently unclear but is unlikely to be before end 2018. PMC would obviously prefer that the EOGRTS can proceed before a decision by RAC on the CLH is made, and has therefore requested a **joint meeting between ESTF, PMC, ECHA and KemI** in order to explain the importance of the interaction between the different legislations applying to Ag / Ag substances

  (Post-meeting note: ECHA has been in contact with KemI to see how the various processes under REACH, BPR and CLP can be coordinated. The Swedish came back with the message that they are considering the way forward. ECHA will contact PMC if they have further info.)

3 Ag read-across approaches PMC / ESTF

Cf. slides 7-10 in Annex 1:

- In light of the recent developments related to reproductive toxicity of Ag and the impact of read-across of effects of 'simple' soluble Ag salts to all Ag substances, both PMC and ESTF are looking into strengthening their read-across argumentation. Both read-across approaches are based on the rationale that the silver Ag(1+) cation is the relevant species released from all Ag substances under physiological conditions and potentially exerting the toxicological effect. Both approaches are supported with **bioelution data** but the **bioelution studies performed by ESTF and PMC both have their limitations**. **AP1**
- It is noted that the ESTF release data from 2010 were discussed with ECHA in 2015 and the read-across strategy was accepted by the MS at that time (read-across from high bioavailability substances to lower bioavailability substances).
- It is further noted that all SCAS were tested in powder form and granulometry info would be available for the tested substances.

4 Proposed strategy to strengthen read-across approaches

PMC has an **outline vision for improving its current read-across approach** (cf. slide 11 in Annex 1):

- **Tier 1**: Data-mine existing toxicokinetics (TK) data on major reference substances (published data + PMC / ESTF owned data) to establish the most definitive picture possible of Ag TK based on existing studies;
- **Tier 2**: Improved *in vitro* bridging studies (bioelution testing including intestinal fluids; for which it is predicted that they represent better models for in vivo absorption potential);
- **Tier 3**: Validation of *in vitro* models by *in vivo* TK testing on a limited number of Ag substances, selected based on the results of the *in vitro* testing.

Comments/questions:

- Given KemI's CLH intentions, there is a time concern. PMC has already requested a joint meeting with the different involved stakeholders and regulators to discuss this (see also above).
- It is noted that *in vitro* data alone will not be sufficient to make definitive conclusions on the bioavailability and read-across. On the other hand, it is acknowledged that the currently available *in*

vitro data are not robust enough and inconsistent across PMC and ESTF substance sets which prevents comparison of data. More robust and simultaneously generated *in vitro* data would allow better assessment / comparison. Furthermore, generating *in vivo* data is more time-consuming and first generating *in vitro* data may convince KemI to put the CLH on hold and wait for further *in vivo* data.

- Release data have also been generated by ESTF for Zn but not for other ions present in SCAS.
- In order to make most efficient use of time, it is suggested to **perform tier 1 and tier 2 in parallel**.
- There is general agreement that we should try to pre-agree on new studies with regulators to ensure acceptance: cf. slide 12 in Annex 1.

PMC and ESTF Tox Experts agree that the current read-across approaches are not robust enough and agree in outline with the proposed tiered approach. It is suggested to discuss the full technical plan in a further face-to-face meeting with the Tox Experts. **AP2**

Annexes

1. Slides presented at the meeting

Actions

Table 1. Actions agreed at the 5 July 2018 ESTF-PMC meeting in Brussels

	What?	Who?	When?
1.	Share available PMC/ESTF bioelution data with TE	PMC Sec	ASAP
2.	Organise meeting PMC/ESTF TE to discuss read-across testing strategy	PMC Sec	Nov-Dec
3.	Update silver bioavailability draft strategy document following this call + MISA workshop	PMC Sec	ASAP