Silver Tox Experts meeting EPMF / ESTF

Draft minutes, Brussels, 19 December 2018 (14:00-17:00 CET)

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.

The list of particpants is available in Annex 1. The agenda is available on slide 4 in Annex 2; no remarks / additions.

2 Background and brief update on respective regulatory processes

2.1 Scope EPMF / ESTF

Cf. slide 6 in Annex 2. EPMF adds that the Substance Evaluation by the Dutch CA is now closed. The conclusion document is available via https://echa.europa.eu/documents/10162/c6597a4b-a88f-9bc9-1a23-b8a41772302c. Based on the test data submitted by EPMF, the evaluating Member State agreed with the read-across approach of ecotox data from ionic silver to the nanosilver forms covered in the REACH registration dossier as a worst-case approach.

2.2 Recap situation silver reprotox, challenges and defence

Cf. slides 7-9 in Annex 2. For AgNO3 and elemental Ag, there are currently data gaps under the BPR (for CMR) and KemI indicated that they would like RAC to decide on **Repr** classification before deciding how to address the other data requirements under the BPR. It is noted that in some other cases where there was a data gap, RAC has concluded 'no classification because no data'.

For **genotox**, EPMF has used a weight of evidence approach in the REACH registration dossier. It is noted that a BPR/CLP genotox decision may precede any future actions under REACH on genotox (see also under AOB).

2.3 Draft decision (DD) EOGRTS TP

EPMF received the DD on 18 Dec. Based on the decision-making process (cf. slide 10 in Annex 2), current estimate for receiving the final decision is June 2019 at the earliest.

In the DD, the **TP is accepted with the test design and test article as proposed by EPMF** (cf. slide 11 in Annex 2). EPMF has 24 months after receiving the final decision to submit the test results.

EPMF would prefer that the EOGRTS can proceed before a CLH decision is made by RAC and has requested a joint meeting with the involved stakeholders and regulators through ECHA, to see how the various processes under REACH, BPR and CLP can be coordinated. ECHA has been in contact with KemI, who is currently considering the way forward. As soon as ECHA has further information, they will contact EPMF. **AP1**

3 Ag read-across

3.1 Brief summary current Ag read-across approaches

Cf. slides 13-16 in Annex 2 and background documents sent before the meeting. It is noted that ESTF originaly submitted the dossiers for the SCAS in 2007/2008. A collective approach was taken at that time with all SCAS being supported by the same dataset and with release data supporting this read-across approach. At the time, these data were considered sufficient for read-across and available studies on the zeolites support this read-across.

3.2 Learnings from first MISA workshop (2 Oct 2018)

Cf. slide 17 in Annex 2. For more information on MISA, see https://www.reach-metals.eu/metals-and-inorganics-sectoral-approach-misa. It is noted that the MS are aware of the MISA framework and which metals are included.

3.3 Strategy to strengthen Ag substance read-across

Tier 1: Data-mining existing TK data

M. Raffray presented the preliminary findings of the ongoing TK data-mining project (cf. slides 18-35 in Annex 2). Comments/additions:

- There is a small dataset for Ag and Ag substances (< 20 key & supporting studies) and a **clear data gap on elemental Ag**.
- AgNP bioavailability (ranging from 0.9 to 3.4%) is higher than expected.
- AgAc has somewhat higher bioavailability than AgNO3 even though it has a lower solubility.
- The ESTF elemental Ag form tested for release is not a nanoform but is not considered representative anymore for ESTF's elemental Ag.
- **Uptake AgNP versus ionic Ag**: it looks as if for AgNP, there is contribution from dissolved Ag (which would also partly explain the conflicting data on AgNP TK) and from particles that may be taken up (agglomeration in the stomach, deagglomeration in the intestine). A further complication is that ionic Ag in physiological media will form secondary AgNP (in the presence of proteins). This means that uptake is ionic + nano + dynamic. Current hypothesis is that AgNP behaves as ionic Ag, so it is **suggested to group AgNP with the Ag salts / ionic Ag and form a separate group for 'bulk' elemental Ag**. This approach will have to be confirmed by further *in vivo* TK testing.
- Full steady state is evident by 14 days exposure (90% by 7 days) so it is suggested to perform **14d *in vivo* tests**.
- ESTF will follow up on TK information in SZZ dossier (tissue levels in rats). **AP2**
- There is a lack of data on Ag TK in humans. It is noted that oral absorption in humans might be higher than in the rat because of higher transit times.
- Slide 33 in Annex 2 summarises why **further bioelution testing for Ag substances does not make sense** and why bioelution is not a good predictor of bioavailability for Ag substances (gross oversimplification of actual situation).
- There are other models that have been used to predict Ag TK: cf. slide 34 in Annex 2 on the **Ag PBTK model** developed by ETH Zurich, and applied to rats and human TK. This could be a way forward instead of further bioelution testing.

Full reference: Bachler et al., 2013. A physiologically based pharmacokinetic model for ionic silver and silver nanoparticles. International Journal of Nanomedicine 8: 3365-3382. [Note that additional details on the model are provided in a separate supplementary data file available from the journal website].

Tier 2: Support of existing data with *in vitro* testing

- As stated under Tier 1, further bioelution testing is not considered the best way forward for Ag substances.
- It is suggested to **explore the PBTK model** in parallel to *in vivo* testing. In first instance, we will need an independent opinion on the validity of the model. George Loizou is mentioned as expert in the field we could contact, but there may be others (**AP3**).
- The model needs to be fed with substance specific information: this will be a challenge for the elemental Ag 'bulk' form (model needed for AgNP, elemental 'bulk' Ag and ionic Ag).

Tier 3: *In vivo* TK testing

- All agree that further *in vivo* TK testing will be needed for elemental Ag and some Ag substances.
- A **14d comparative TK study** is suggested (steady state).
- It is suggested to not measure endocrine parameters in the TK study.
- Suggested **test substances for *in vivo* testing**:
  - Relevant to EPMF and ESTF: elemental 'bulk' Ag (micron-sized form without nano), AgAc, AgNO3 and AgCl.
  - Relevant to EPMF: elemental AgNP, Ag2O as poorly soluble compound.
  - Relevant to ESTF: SZZ, SSZHP
- It is suggested to make an overview table with phys-chem data available for all Ag substances in scope. **AP4**
- It will need to be checked which form of **elemental 'bulk' Ag** is most representative for the market (REACH + BPR) (**AP5**). Alternatively, a screening study could be done first, checking ionic release for different particle sizes.
- A separate follow-up detailed discussion on the test design of the TK study will be needed. **AP6**
- ESTF notes that they would need KemI's approval before they go ahead with *in vivo* testing. EPMF will explore the possibility to discuss the testing program with ECHA through the MISA framework.
- If AgNO3 is included in the testing program, there may be a possibility to delay KemI saying that new information is being generated.

4 AOB

ESTF is currently considering to do further *in vitro* genotox testing and will keep EPMF informed of further actions (**AP7**).

Annexes

1. List of participants
2. Slides presented at the meeting

Actions

Table 1. Actions agreed at the 19 December 2018 Ag Tox Experts meeting EPMF/ESTF in Brussels

	What?	Who?	When?
1.	Follow-up ECHA-KemI contact.	EPMF Secretariat	Jan 2019
2.	Check TK information in SZZ dossier.	ESTF	Jan 2019
3.	Check if any contacts would be able to contribute further thoughts on the PBTK model validity.	All	Jan 2019
4.	Make overview table with available phys-chem data for all Ag substances in scope.	EPMF + ESTF Secretariats	Jan 2019
5.	Check which form of elemental 'bulk' Ag is most representative for the market (REACH + BPR). Check available granulometry data. Ask members to identify elemental 'bulk' Ag form that has the biggest market share for them.	EPMF + ESTF Secretariats	Jan 2019
6.	Organise follow-up detailed discussion on the test design of the TK study	EPMF Secretariat	Jan 2019
7.	Keep EPMF Secretariat informed of further actions re genotox testing.	ESTF	As needed
8.	Check if Dow lab is able to perform EOGRTS studies and inform the EPMF Secretariat.	I. Watt	Jan 2019

Annex 1: Participants

EPMF:

1. Katrien ARIJS — Consultant for EPMF (ARCHE, Belgium)
2. Arno BUTHE — Heraeus (Germany)
3. Marie-Laure LEDRICH — Consultant for Traxys (Luxembourg) - *via conference call*
4. Olga LEMKE — BASF (Germany) - *via conference call*
5. Jelle MERTENS — EPMF (Belgium)
6. Mark RAFFRAY — Consultant for EPMF (Raffray Biosciences Ltd, United Kingdom)
7. Nissanka RAJAPAKSE — Johnson Matthey (United Kingdom)
8. Steven VERBERCKMOES — Umicore (Belgium)

ESTF:

1. David ANDREW — Consultant for ESTF (ERM, United Kingdom)
2. Sage BEGOLLY — Dow (United States) - *via conference call*
3. Rob COLLINS — Tarn-Pure (United Kingdom)
4. Andrew GOODYEAR — Consultant for ESTF (ERM, United Kingdom)
5. Carol MACKIE — Consultant for Tarn-Pure (RCL, United Kingdom) - *via conference call*
6. Germaine TRUISI — Thor (Germany)
7. Ian WATT — Dow (United Kingdom)