



Silver Tox Experts (TE) Call

Draft minutes, Call 18 June 2019 (10:00-11:30 CET)

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 on slide 3 in Annex 2. No remarks / additions; agenda approved.

1.4 Approval of the minutes of the last call (23 Apr) and status of action points

Minutes of the call of 23 April were approved. A table with the status of the action points from this meeting is available on slide 4 in Annex 2. All action points have appropriately been addressed/are ongoing, or will be discussed during the call. Comments/additions:

- For the estrogen measurements in the AgAc gut biome study (AP3 from 23 Apr TE call), it is suggested to have this done somewhere else if too difficult for prof. Lison to perform. Depending on progress/results, we may also need to include this measurement in the EOGRTS. **AP1**
- Some publications on the BASF metabolomics project (shared by O. Lemke immediately after the call) are available in Annex 3.

2 Process and timing EOGRTS TP

Updated process and timeline is available on slide 5 in Annex 2:

- TP accepted so far by ECHA, with **30 months** deadline mentioned in the amended DD to submit the requested information.
- ECHA only received **PfAs from the Netherlands**, suggesting addition of the **DNT** cohort (cohorts 2A and 2B) to the study design; EPMF comments were submitted by 20 May 2019.
- Eurométaux informed us that MSC agreement on the Ag TP was achieved by **written procedure**. The MSC chair will give a short debrief on the written procedural cases during the MSC meeting of 24-27 June. We should receive the final decision shortly after.

(Post-meeting note: Final decision received and forwarded to the Ag TE/WG on 27 June; TP accepted with addition of the DNT cohort.)

3 Selection CRO for TK / DRF / EOGRTS testing

Based on the outcome of the 23 Apr TE call, a draft test design for the TK, DRF and EOGRTS testing was sent to Charles River, Citoxlab, Covance, Envigo and LPT, together with a request for offers. After careful consideration of the offers and taking into account the experience and availability of the different CROs,



the EPMF Secretariat recommended to select **Envigo** (now part of Covance) for the testing: cf. slide 7 in Annex 2.

This recommendation was sent to the Ag WG and no objections were received. The TE are also comfortable with the choice of Envigo. The **timing** of the testing as mentioned in the draft Envigo proposal is summarised on slide 8 in Annex 2. The EPMF Secretariat will finalise the contract ASAP to ensure timing is fixed and we do not risk losing our timeslot for the EOGRTS. **AP2**

It is mentioned that, following the merge of Envigo and Covance, it would be useful to benefit from Covance's / Arcinova's experience on TK / Ag analysis where possible.

4 Ag DRF/TK testing

- **Dietary admin dosing issue:** cf. slide 9 in Annex 2. Following the discussion during the last TE call on the discrepancy between the nominal and the actual dosing in the AgAc gut biome study, food consumption and dietary incorporation levels from the study were further examined. A gradual decrease in achieved dosing over time (from ca. 100% of the nominal dose at the start of the experiment to ca. 60% (female rats) and 50% (male rats) towards the end of the experiment) was observed because of body weight gain of the rats. This possible change in dosing is something to take into account during the DRF and EOGRTS testing as well and this can be partly dealt with through adapting the dietary incorporation levels over the course of the studies. The TE agree it would make sense to make this adjustment for the DRF/EOGRTS. **AP4**
- The TE agree with the **adapted study design for the DRF** as suggested by Envigo (cf. slide 11 in Annex 2), with extended dosing (15 wks instead of 9 wks) to allow F1 offspring to consume the treated diet already in the DRF. This was suggested to avoid the risk in the actual EOGRTS of the doses being toxic for the F1 offspring.
- It is noted that, taking into account above adaptation and the test parameters measured in the test (e.g. histopath not included), the **DRF will not be a fully TG conformant test** and as such, not suitable for inclusion in the REACH dossier. Since the main purpose of the study is to assist in dose setting of the main EOGRTS and the test has been specifically designed to serve this purpose, the TE agree this is not a major issue.
- For the **TK testing**, the TE agree that we should go for the 5 animals per group design. The OECD 417 TG mentions at least 4 animals per group and we want to ensure that the results are statistically sound.
- **GLP status** of studies: the TE agree that for the DRF, non-GLP is acceptable but for the TK study, GLP is preferred.
- Other remaining questions, comments and suggestions on the test design as discussed during the call (and received from the TE and Lindsay Aveyard after the call) have been directly added in the proposal: cf. **Annex 4**.
- A face to face meeting with Envigo will be organised in August, with the study monitors. For now, the period 26-30 August looks best. **AP4**
- The selection of the test items and the dosing for the TK testing will be further discussed in August.



Annexes

1. List of participants
2. Slides presented at the call
3. Publications BASF metabolomics study
4. Envigo proposal for Ag TK, DRF and EOGRTS testing, with remaining comments / questions to Envigo directly added in the proposal (as sticky notes)

Actions

Table 1. Actions agreed at the 18 June 2019 Ag Tox Experts call

	What?	Who?	When?
AgAc gut biome study			
1.	Follow-up with prof. Lison: <ul style="list-style-type: none"> • Ag localisation in brain, testis and kidney with AMG; • Histopath uterus and ovaries samples (via prof. Marbaix); • Offer for estrogen analysis (or have this done somewhere else if too difficult for prof. Lison to perform). 	EPMF Sec	ASAP
Ag TK / DRF / EOGRTS testing			
2.	Finalise contract with Envigo for Ag TK / DRF / EOGRTS testing	EPMF Sec	ASAP
3.	Provide offer for TK study monitoring	M. Raffray	By end July
4.	Fix face to face meeting with Envigo in August. Points for discussion: <ul style="list-style-type: none"> • Possibility to adjust dietary incorporation levels during studies / experience with dietary admin for EOGRTS and evolution food consumption; • Comments added to the Envigo proposal (cf. Annex 4). 	EPMF Sec	Meeting fixed for 28 August
5.	Check particle size, purity of elemental Ag forms in REACH dossier + ensure sample analysis before testing	EPMF Sec	ASAP
6.	Agree on: <ul style="list-style-type: none"> • Dose levels for each substance for TK testing; • Selection test items; • Participation BASF metabolomics project. 	Ag TE	August 2019



Annex 1: Participants

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Arno BUTHE, Heraeus (Germany)

Eliot DEAG, Johnson Matthey (United Kingdom)

Juergen HANICH, Ferro (Germany)

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Mark RAFFRAY, Consultant, Raffray Biosciences Ltd (United Kingdom)

Nissanka RAJAPAKSE, Johnson Matthey (United Kingdom)