Silver Work Group meeting

Minutes, Brussels, 8 October 2019 (11:00-12:45 CET)
Chair: France Capon (EPMF) in the absence of Clémence Siret (SAFT, France) and Rob Garrett (Ames, UK)

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 4 in Annex 2. No remarks / additions; agenda approved. In the afternoon there will be an internal workshop on CLH advocacy, chaired by Rud Pedersen.

1.4 Approval of the minutes of the last meeting (2 April 2019) and status of action points

No remarks / additions; minutes of the meeting of 2 April were approved. A table with the status of the action points from this meeting is available on slides 6-7 in Annex 2. Some action points related to the WFD prioritisation have been postponed due to other priorities. All other action points have appropriately been addressed / are ongoing where possible, or will be discussed in this meeting.

2 Silver reproductive toxicity

2.1 EOGRTS Testing Proposal: final decision and timeline

EOGRTS TP process and timeline is available on slide 9 in Annex 2. The original draft decision (DD), in which the TP was accepted with the test design / test substance as proposed, was received in December 2018. During the subsequent process, the Netherlands submitted proposals for amendments (PfAs) and suggested to add the developmental neurotoxicity (DNT) cohorts 2A and 2B to the EOGRTS test design. During the commenting period, EPMF acknowledged that some publications provide limited evidence of CNS neuropathological findings following Ag exposure but concluded that based on weight-of-evidence (WoE) considerations, it has not been demonstrated that Ag meets the evidential triggers for DNT concerns, i.e. involving findings from scientifically robust studies which also meet the thresholds for severity (adversity). However, EPMF stated that it was willing to include the DNT cohorts in the EOGRTS test design if deemed necessary by the European regulators. The TP was then handled via the written procedure and the final decision was received in June 2019, requesting the **EOGRTS with DIT and DNT cohorts**. The EOGRTS test results are to be submitted by **3 January 2022**.

The content of the final decision is summarised on slides 10-12 in Annex 2. Regarding our **read-across approach** (read-across from silver acetate (AgAc) to all substances forming ionic silver), ECHA has stated in the decision that it is 'plausible' for the purpose of the TP evaluation (standard wording) but that the eventual validity of the read-across approach will be reassessed once the EOGRTS results are submitted. ECHA also refers to the **REACH information requirements for nanomaterials** in the final decision and brings our attention on the particular concerns identified by the PfAs resulting from studies on Ag nanoparticles (AgNPs). This stresses the importance of the TK program (cf. also agenda point 3). To ensure compliance of the Ag REACH dossier concerning AgNPs by 1 January 2020, it is proposed to

include a RSS for AgNPs in the dossier referring to the ongoing EOGRTS for AgAc and the ongoing TK work for read-across. **The WG agrees to the suggested dossier update for AgNPs**. AP1

Regarding the **dose-level setting**, the DD states that the highest dose level shall aim to induce systemic toxicity and dose level selections shall be clearly justified. If there are no relevant data for dose level setting, the results of a dose range finder (DRF) should be reported with the main study. EPMF reviewed the available Ag dose level versus effect info, concluded that this is insufficient for definitive dose setting for the EOGRTS and agreed to perform a DRF study.

2.2 EOGRTS: test design and testing preparation Covance

Cf. slides 13-16 in Annex 2:

- Envigo (now **Covance**) was selected for the TK, DRF and EOGRTS testing because of their relevant experience and availability. Mark Raffray and Lindsay Aveyard have been contracted as study monitors for the TK and reprotox testing respectively. Several Tox Experts (TE) calls and meetings have already taken place to decide on the test design.
- The **draft timeline for the testing** is summarized on slide 14 in Annex 2. This timeline assumes a fully GLP compliant TK study (cf. also discussion under agenda point 3).
    - For the **TK study**, the original aim was to have the results available in time for the RAC discussion on the silver nitrate ($AgNO_3$) CLH in order to support our read-across approach (cf. also timeline CLH on slide 24 in Annex 2). Eurométaux informed us that the accordance check for the $AgNO_3$ CLH is finalised (although ESTF believes it is not), meaning the public consultation could start any time now. However, given RAC's workload (currently 15 public consultations are ongoing, including 3 on metals), the public consultation will probably not start before the end of the year. The usual time between the start of the public consultation and the first RAC discussion is 4 to 5 months, so the **first RAC discussion on the $AgNO_3$ CLH will most likely not take place before June 2020**. Timing may be tight to have the TK results by June 2020 but it is anticipated that more than 1 discussion at RAC will be needed to conclude on the $AgNO_3$ CLH.
    - For the **reprotox testing**, the EOGRTS report should be available June 2021 (but preliminary EOGRTS results will be available earlier in 2021, i.e. between Feb-Apr), which should be sufficient for submission of results by 3 January 2022. It is noted that, in case of a worst case outcome of the EOGRTS and update of the DNEL, classification, ES etc. is needed, this will take several months. The EPMF secretariat will already look at planning for this (AP2). It is further noted that interim reporting during the testing will be very important for timely decision making and to timely anticipate needed dossier updates (AP3). In case of any test issues at Covance, it may also be useful for the Tox Experts to go on site. It is suggested to ask Covance to report in a format suitable to enter into IUCLID (AP4).
- The test design of the **DRF study** (cf. slide 15 in Annex 2) is based on OECD TG 422 but with several adjustments to increase the confidence in the main EOGRTS.
    - **Longer exposure** of the F1 offspring was suggested to ensure they will consume the treated diet in the DRF study (this to avoid risk of doses being toxic for the pups in the main EOGRTS). Longer pre-pairing exposure of the F0 animals was suggested to allow possible effects on fertility being picked up already in the DRF study.
    - A total of 4 **dose levels** was suggested for the DRF to ensure proper identification NOAEL/LOAEL. Dose levels are based on available Ag dose level versus effect info (175 - 55 - 13 - 4 mg AgAc/kg bw/d).

- **Adjusted ppms** (i.e. adjustment of the dietary inclusion levels) were suggested for the DRF study and main EOGRTS pre-mating and post-weaning in order to maintain dose levels as close as possible to target levels. Although there is still a risk of overdosing F0 females during lactation (because of higher food intake), it was agreed to not adjust ppms during lactation as this is very difficult logistically. **The WG suggests the Tox Experts to re-discuss adjusted ppms during lactation to avoid the risk of overdosing**, e.g. there is the possibility to mix treated diet with untreated diet during this period. **AP5**
- **Additional parameters** (e.g. Cu, Se, ceruloplasmin and glutathione peroxidase measurements, Ag measurement in the brain) have been integrated in the DRF study for robustness.

- The test design of the **EOGRTS** (cf. slide 16 in Annex 2) is based on OECD TG 443 and will be further refined based on the results of the DRF study.

3 Silver read-across and TK study

Cf. slides 18-21 in Annex 2:

- Since the available data on Ag TK is fragmentary and overall confidence level is low, it was previously agreed a **comparative *in vivo* TK study** (aligned with OECD TG 417) is essential to support our read-across approach. Key substances to be included in the TK testing are: AgAc, $AgNO_3$, elemental Ag (≥ micron-sized) and elemental nanoAg. Ideally, the study would allow differentiation between elemental Ag and ionic Ag, and elemental Ag and nanoAg.
- The **selection of the elemental Ag (≥ micron-sized) and elemental nanoAg test items** for the TK study is currently under discussion by the Tox Experts. Since the smallest REACH registered Ag nanoform is not available for testing, the Tox Experts are considering the use of a certified reference material (CRM) instead. It is noted that we will need to be careful in the selection of the elemental micron-sized Ag form to be tested for TK. Current strategy is to test the worst case form in terms of bioavailability. Once the results from the TK study are available, we can discuss the strategy for defence of the massive Ag form. It is suggested that, in addition to the TK results itself, data on skin penetration may be helpful here. **AP6-7**
- **GLP compliance** TK study: during discussions with Covance and the Tox Experts, several options were discussed (cf. slide 21 in Annex 2). **The WG agrees to go for the fully GLP compliant TK study if technically feasible**, as this would strengthen the credibility and the use of the study for advocacy purposes. Since the method development needs to be finalised first before we can fully look into what is needed for validation, the Tox Experts will review how the progress has been made after the method development and confirm the final details of the validations at that point. Ideally we would like to adhere to full validation/GLP compliance but if Covance struggles with the method development for the tissue analyses, we do not want the study to be too much delayed because of this so the validation will be re-discussed after the method development. **AP8**

4 CLH proposals silver nitrate and silver

A recap of CLH proposals made by Kemi for the reprotox endpoint for Ag substances is available on slide 23 in Annex 2. Kemi has submitted CLH proposals for silver nitrate in December 2018 (accordance check finalised) and for silver in May 2019 (still in accordance check phase) with a Repr Cat. 1B classification. As stated under agenda point 2.2, the **public consultation on these substances will probably not start before the end of the year**. 18 months after the start of the public consultation, the RAC opinion has to be available (cf. timeline on slide 24 in Annex 2), i.e. probably before the availability of our EOGRTS test

results. The timing uncertainty of the CLH process complicates our planning. This has been highlighted to ECHA through the MISA framework and ECHA took note.

It is noted that it will be important to get **downstream users (DUs) involved** to make an argument about exposure. The delay on the start of the public consultation may give us sufficient time to mobilize DUs, some of which are quite influential. Reference is made to the DU workshop of 7 November (https://www.epmf.be/epmf-silver-workshop/).

A comment is made on the importance of following up on the substance definition of elemental Ag in the CLH proposal. **AP9**

4.1 Science defence

Cf. slides 25-30 in Annex 2. Comments / additions:

- It is noted that possible incidences of **skin sensitisation** following Ag exposure may be related to Ni impurities in e.g. Ag jewellery (**AP10**). We may get further relevant data from DUs (e.g. a discussion with the French jewellery association is planned 22 October).
- **The WG agrees to update the Skin Corr. classification of solid $AgNO_3$ to Cat. 1A** based on the available *in vitro* data (cf. slide 26 in Annex 2), and to include this evidence in our comments to the CLH proposal as it is further proof of the overall weak assessment Kemi has performed in the CLH proposal. **AP11**
- Following the EU CLP tox mixture rules, the Skin Corr. 1A classification for the solid $AgNO_3$ form implies a Skin Corr. 1A classification also for solutions ≥ 5% $AgNO_3$ (and a Skin Irr. 2 classification for solutions with 3-5% $AgNO_3$). It was suggested by one of the WG members to undertake skin corrosion testing of solutions ≥ 5% $AgNO_3$ to further refine the classification. **The WG currently sees no need to perform additional skin corrosion testing of solutions ≥ 5% $AgNO_3$.**

4.2 Impact assessment

Cf. slides 31-35 in Annex 2. Comments / additions:

- Under the **new CLH process via delegated act**, there is no public consultation after the RAC opinion anymore. Furthermore, there is no vote at the REACH committee, meaning less power for the Member States.
- The delegated act can be accompanied by an **impact assessment** but how to trigger this impact assessment is currently still unclear. You may have to already demonstrate that there is a significant economic, environmental or social impact before the Commission carries out an impact assessment (political decision depending on weight of issue). Therefore, EPMF decided to already start an impact assessment of the possible Repr 1B classification. Several offers were requested and EFTEC was selected because of their experience with Co and Ni.
- At the November DU workshop, EPMF will ensure as many people as possible submit comments, even if an impact assessment is not triggered. Different sectors have been invited to the workshop (automotive, solar panels, biocides, jewellery, silverware, investment, electronics, …). WG members are encouraged to invite possibly influential downstream users. **AP12**
- The data collection will be done via questionnaires but also via interviews. **AP13**

5 Workplan and budget 2020

Cf. slides 37-39 in Annex 2. **The WG agrees to the proposed 2020 draft budget.**

6 AOB, next meetings/calls and closing remarks

The WG agrees to the addition of uses for disilver sulphate (cf. slide 41 in Annex 2). Since this is a 1-10 t/a substance and there is no CSR (and no ES), this is a limited dossier update. **AP14**

Annexes

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

Actions

Table 1. Actions agreed at the 8 October 2019 Ag Work Group meeting in Brussels

	What?	Who?	When?
1.	Include a RSS for AgNPs in the Ag dossier referring to the ongoing EOGRTS for AgAc and the ongoing TK work for read-across and submit dossier update	EPMF Sec with Ag LR	By 1 Jan 2020
2.	Draft internal Gantt chart on different steps for dossier update following EOGRTS results, sequencing the updates in the most efficient way	EPMF Sec	Q4 2019
3.	Draft Gantt chart to highlight when Tox Experts (TE) and WG members must be available for review and commenting of the EOGRTS results and schedule regular TE meetings / calls for interim reporting / discussion of test results	EPMF Sec with Ag TE & study monitors	When detailed study plans are available
4.	Ask Covance to report testing outcomes in format suitable to enter into IUCLID	EPMF Sec with study monitors	Q4 2019
5.	Re-discuss adjusted ppms during lactation in DRF + EOGRTS to avoid the risk of overdosing	EPMF Sec with Ag TE & reprotox study monitor	Q4 2019
6.	Select elemental Ag (≥ micron-sized) and elemental nanoAg test items for TK testing	EPMF Sec with Ag TE & TK study monitor	ASAP
7.	Discuss strategy for defence of massive Ag, considering available data on skin penetration	Ag WG	When results TK study are available (Q2-Q3 2020)
8.	Confirm final details of the TK tissue analyses validation	EPMF Sec with Ag TE & TK study monitor	After method development for TK tissue analyses
9.	Check which elemental Ag forms are covered exactly under the BPR / in the elemental Ag CLH proposal	EPMF Sec	When elemental Ag CLH proposal is available
10.	CLH comments: assess the potential link between the skin sensitisation classification proposal and the presence of Ni impurities	EPMF Sec	Q4 2019
11.	Include *in vitro* skin corrosion test data in $AgNO_3$ dossier and update skin corr. classification of solid form / solutions ≥ 5% $AgNO_3$ to Cat. 1A + include evidence in CLH comments	EPMF Sec	Q4 2019
12.	Invite possibly influential downstream users to the November DU workshop	Ag WG	ASAP

13.	Indicate when WG members should be available for input on the impact assessment	EPMF Sec with EFTEC	Q4 2019
14.	Add disilver sulphate uses to the REACH registration dossier	EPMF Sec	After 3 Dec Assembly