



# Meeting EU Silver Task Force (ESTF) – Precious Metals Consortium (PMC)

Minutes, Brussels, 5 July 2018 (09:00-13:00 CET)

## List of participants

- |                           |                     |                |
|---------------------------|---------------------|----------------|
| 1. <b>Katrien Arijs</b>   | Consultant for PMC  | Belgium        |
| 2. <b>Andrew Goodyear</b> | Consultant for ESTF | United Kingdom |
| 3. <b>Jelle Mertens</b>   | PMC                 | Belgium        |
| 4. <b>Ian Watt</b>        | ESTF                | 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. **AP1**

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

### 2 Update on respective regulatory processes

#### 2.1 PMC

Cf. slides 6-13 in Annex 1. Remarks / additions:

- On slide 6 (**scope** REACH vs BPR), 2 substances were missing for ESTF (total of 10 silver containing active substances (SCAS) in scope; AgCl is a new ESTF substance); slide corrected in Annex. The substance 'silver (reaction mass with TiO<sub>2</sub>)' is a nanoform. Discussions are currently ongoing on the substance identity of silver phosphate glass (which may result in this substance being split into several substances).
- The scope of the ongoing **REACH substance evaluation (SEv)** is limited to the environment. Although ESTF is interested in additional Ag ecotoxicity tests performed by PMC from a scientific viewpoint, they note that the environmental endpoints under the BPR are sufficiently covered, mainly driven by literature data and that this is sufficient to pass the environmental risk assessment (which is driven by the sediment compartment) in the available Competent Authority Reports (CARs). From a regulatory viewpoint, their interest in additional ecotoxicity test results is therefore rather limited (but data sharing in this respect is not ruled out as ESTF would support regulatory alignment of endpoints).

*(Post-meeting note: The results of the SEv soil ecotox testing have been published earlier this year: Bollyn J., Willaert B., Kerré B., Moens C., Arijs K., Mertens J., Leverett D., Oorts K. and Smolders E. (2018), Transformation-dissolution reactions partially explain adverse effects of metallic silver nanoparticles to soil nitrification in different soils. Environ Toxicol Chem. <https://doi.org/10.1002/etc.4161>)*



## 2.2 ESTF

Cf. slide 15 in Annex 1. Remarks / additions:

- The dossiers for the SCAS were originally submitted in 2007/2008. A **collective approach** was taken at that time with all SCAS being supported by the same dataset. The 2012 CAR for SZZ by Rapporteur MS Sweden (Kemi) contained an assessment of this collective approach. Now, Sweden is assessing each SCAS individually and it is unclear what **read-across approach** they want to take.
- ESTF received the **draft CARs** (together with the draft CLH proposals) for SCZ, SZ and SSZHP in June 2017.
- The **final BPC opinion** for SZZ, SCZ, SZ and SSZHP is expected in October 2018, meaning that the process for these substances is exceeding the original timeline substantially.
- Even though the **draft CLH proposals** for SCZ, SZ and SSZHP have been submitted by Sweden more than a year ago, the **public consultation** still has not started. However, since the proposed CLH for these SCAS does not meet any of the exclusion criteria for active substances under the BPR (CMR Cat. 1, ED, PBT/vPvB), the CLH process has no impact on the timing of the BPC opinion for these substances. Furthermore, there is no clear deadline for the ECHA accordance check during the CLH process. Therefore, the timeline for the public consultation is still unclear. **AP2**
- PMC has submitted a testing proposal (TP) for an extended one-generation reproductive toxicity study (**EOGRTS**). The outcome of this study (which will likely not be available before 2020) may have an impact on the Repr. classification of the SCAS. What happens for those SCAS where the BPC opinion has already been concluded by then? Under the BPR, an authorisation for an active substance is normally valid for 10 years, then it can be renewed. However, at product authorisation level, there is a mechanism to overrule this authorisation for substances that meet the exclusion criteria after the BPC opinion has been concluded (obligation to inform the authorities if new data become available on adverse effects).

## 3 Update on ED process and outcome

Cf. slides 17-18 in Annex 1. Remarks / additions:

- It was noted that SZZ and SSZHP were the very first biocide substances to be evaluated by the ED EG.
- The ED EG did not reach a conclusion at the meeting but a **written response from the experts** was asked. Comments were received from 3 MS (not clear which MS) and from the applicant. ESTF submitted comments (stating that available data are sufficient to conclude ED is not a concern for the SCAS) but received no feedback.

*(Post-meeting note: ESTF sent further information regarding the MS comments:*

- *One MS proposed an in vitro testing battery to get more mechanistic information and then a peripubertal or a Hershberger assay to confirm the effects in vivo.*
- *Another MS questioned the usefulness of in vitro data due to the possibility that silver ions precipitate together with chlorine ions from the culture medium to form insoluble AgCl and may not enter the cells or show a representative toxicity pattern. In their view, in vivo mechanistic studies in rodents (level 3 and/or level 4 tests) should be considered since the substance has been classified as Repr 2. They also considered it necessary to address the*



*issue for non-target organisms by performing studies according to OECD TG 229 and OECD TG 231.*

- *The third MS as well as the applicant stated that existing data is sufficient to conclude that the substance does not fulfil criteria for endocrine disruption. Considering that there were no clear indications of an endocrine potential in the existing studies and that there is a fertility study available in which ED related parameters are sufficiently investigated according to the latest version of OECD 416,*
- *The eCA does not favour further in vivo testing. The lack of thyroid hormone analyses was considered of low concern in the absence of effects on thyroid weight or histopathological changes in the other studies available. Therefore, no further studies are requested for the T modality.)*
- The outcome from the meeting came on Friday 29 June in the form of an **updated CAR for SZZ** from Sweden. For HH effects, it was stated that for SZZ there is no ED concern or requirement for further testing. For environmental effects, the available info (i.e., mainly public literature data) do not strongly indicate an ED potential and criteria are thus not considered fulfilled. **AP3**
- It is noted that the ECHA ED guidance changed around the ED EG meeting. According to that guidance, ESTF has HH data that should be sufficient to conclude on HH ED effects of SZZ. **AP4**
- For SZZ no further testing is proposed and a similar conclusion is expected for SSZHP. The ESTF consider it important to build a WoE approach for the absence of ED effects of SCAS and will perform a literature survey for **environmental ED effects** of all SCAS (for all active ingredients like Ag but also Cu etc.). Further testing may be needed. The ESTF will make a formal assessment of ED properties for all SCAS, to be addressed in the following CARs.
- PMC notes that **Eurométaux performed a literature assessment of ED for metals**. However, in literature, often mixture exposures are tested, and if only 1 metal is tested, this is mostly at very high doses where you also see toxicity effects so the ED effects are not relevant anymore.
- Under **REACH**, no data for ED are required for the environment. For HH, you have to include a screening assessment in OECD TGs 407/421/422 assays.

## 4 Status of PMC REACH testing proposal

Cf. slides 20-26 in Annex 1. Remarks / additions:

- Slide 20 shows the tentative (shortest) timeline of the EOGRTS TP: the TP is now under evaluation by ECHA and PMC is waiting for the **Draft Decision (DD)**, which will not be sent before August 2018.
- PMC's opinion is that, despite the available literature data - including the important study by Sprando et al. 2017 (**AP5**) - **data-gaps with regard to the reproductive toxicity potential of silver still remain**, and that an EOGRTS would provide a superior end result to hazard assessment. It is noted that, even if the EOGRTS TP is accepted, the outcome of the EOGRTS is highly unpredictable and the risk of classification of Ag as Repr cat. 1B still exists (which would have SVHC implications under REACH, and would trigger exclusion under the BPR).
- Even though further research on the reproductive toxicity potential of ionic silver has been performed, there is still **uncertainty on the mode of action (MoA)**, including whether indirect effects on reproductive parameters may be acting as important confounders. For instance, ionic silver is acknowledged to be a highly active microbiocide, and effects on the gut microbiome at silver treatment levels corresponding to those in most recent reproductive toxicity studies have not yet been assessed.



PMC firmly believes that enabling work is needed prior to the EOGRTS dose-setting/study and therefore will perform a study with silver acetate (AgAc) on rats to evaluate if significant **gut microbiome effects** could occur at dose levels relevant for the EOGRTS study: cf. slides 25-26 in Annex 1.

- There was some discussion on **read-across from AgAc data**:
  - ESTF wonder if it may be useful to check not only the effects of AgAc on the gut microbiome but also of AgCl or AgNO<sub>3</sub>, to check if different Ag compounds result in different toxicokinetics (TK) / effects. PMC considers this not feasible in the current study design.
  - In the TP, PMC has proposed AgAc as test substance because it is a soluble Ag salt (known to exhibit satisfactory bioavailability via the oral route) and it has been commonly utilised in a variety of published tox studies as soluble Ag reference compound, and is so referenced for read-across purposes in the REACH dossiers for Ag and Ag compounds. PMC expects testing outcomes from studies with AgAc to be fully applicable to ionic silver (Ag<sup>+</sup>) irrespective of the donor Ag substance releasing this ion.
  - ESTF consider substances such as SZ, SCZ, and SZZ carriers of metallic silver and these substances are not considered to exhibit the same bioavailability as AgAc. For silver salts such as AgNO<sub>3</sub>, this is a different issue.
  - AgNO<sub>3</sub> is a data-light substance, and read-across has been done from other Ag substances. This because AgNO<sub>3</sub> is considered corrosive / highly irritant to mammalian tissues. However, ESTF has performed a 28d oral (gavage) RDT study with AgNO<sub>3</sub> showing that corrosivity is not such a big issue as previously assumed, but also that read-across between other SCAS is justified.
  - ESTF would consider generating TK data on different SCAS and AgAc, to prove different bioavailability of different Ag (containing) substances.
- PMC believes that the Sprando et al. 2017 study has been assessed by Sweden in the CLH proposals for SZ and SCZ, although it is not referenced as such.  
*(Post-meeting note: The Sprando et al. 2017 study is referenced as 'Literature data, silver acetate' in the CLH proposal for SZ on pages 59-60 and in the CLH proposal for SCZ on pages 55-56.)*
- ESTF will check with the US STF if they have assessed the Sprando et al. study. **AP6**
- Reference is also made to the NTP study on AgAc (Boudreau et al. 2016).
- As far as ESTF is aware, the Babu et al. 2016 study has never been mentioned by **Sweden**. ESTF also assumes Sweden is not aware of the EOGRTS TP. PMC considers contacting Sweden once the DD is available. ESTF agrees that the knowledge about the EOGRTS should be brought into the BPR process (but could also delay the BPR process).
- **ESTF and PMC agree it is important to consider the impact of the interaction of the different legislations applying to silver substances (REACH / CLH / BPR) and to bring this to ECHA's and Sweden's attention. AP7**

## 5 Other available or proposed toxicology/ecotoxicology testing

Cf. slides 28-29 in Annex 1. Remarks / additions:

- For the environment, ESTF considers their dataset currently sufficient for risk assessment purposes.



- The 4 tox studies mentioned on slide 29 are recent and are individual company data (i.e. not owned by ESTF but by member companies). The first 2 studies were performed with AgNO<sub>3</sub> and are GLP guideline studies.

## 6 Potential for data sharing

ESTF expresses their interest in the new tox data that are being generated by PMC (gut microbiome study + EOGRTS). Also, ESTF considers it important to share advocacy actions. **AP8-9**

## 7 CLH proposals for the SCAS

Cf. slides 33-36 in Annex 1. Remarks / additions:

- For **AgNO<sub>3</sub>**, ESTF received an e-mail from Sweden indicating **possible Repr 1B classification** and the plan to approach ECHA for advice. They also indicated a **potential data gap for C&M effects** but it is not feasible to do additional tests by end 2018 (timing CAR). The potential data gap does not come from the results of the 28d study with AgNO<sub>3</sub> but from a formal requirement to submit appropriate test data. The test doses used in the 28 day study indicate that long term repeat dosing of AgNO<sub>3</sub> is possible (i.e. top dose in 28 day study does not show serious effects which might be expected from substance classified as corrosive).
- Read-across is accepted for SZZ, SZ, SCZ and SSZHP but may be questioned for more soluble Ag compounds (AgNO<sub>3</sub>).
- ESTF thinks it is important to point out the ongoing CLH process for the SCAS to ECHA during the informal discussion PMC will have with them after receiving the DD on the EOGRTS TP. The PMC TP could be the reason why the public consultation on the CLH is postponed? **AP10**

## 8 PNECs under REACH/BPR

Cf. slides 38-47 in Annex 1. Remarks / additions:

- In addition to the ESTF sediment study mentioned on the slides, ESTF also performed a study with natural sediment but this study did not meet the validity criteria, so was rejected by Sweden. The test indicated a much higher endpoint compared to a comparable test with artificial sediment.
- For freshwater, ESTF pass the risk assessment based on their current dataset. For sediment, there are some issues with some of the outdoor uses where there is direct environmental exposure without treatment/removal by an STP.
- Change of PNEC under the BPR: when already approved at BPC level, you can only change the PNEC at the 10 year renewal unless at product authorisation level when there is issue for specific use

## 9 Any other business

To confirm substance identity under the BPR, GLP studies can be waived for so called 'commodity' chemicals if adequate non-GLP data are available (e.g detailed certificates of analysis). Sweden has asked for further data showing that AgNO<sub>3</sub> and metallic Ag are 'commodity' chemicals. PMC suggests pointing out the different uses of these substances as listed on the ECHA dissemination site or checking the report of the Silver Institute.



## 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.	Check if non-disclosure agreement between PMC and ESTF needs to be updated following the absorption of PMC by EPMF end 2018	PMC	Q3 2018
2.	Inquire with Sweden if they have further info on the timeline for the public consultation of the CLH proposals for SCZ, SZ and SSZHP	ESTF	Q3 2018
3.	Share updated CAR for SZZ with PMC	ESTF	Q3 2018
4.	Prepare summary of HH ED data for SZZ and share with PMC	ESTF	Q3 2018
5.	Check if PMC assessment of Sprando et al. study can be shared with ESTF	PMC	Q3 2018
6.	Check with the US STF if they have assessed the Sprando et al. study	ESTF	Q3 2018
7.	Discuss internally possible advocacy actions towards ECHA / Sweden related to the reprotoxicity of Ag and Ag substances	PMC and ESTF	Q3 2018
8.	Keep each other informed on contacts with / relevant info to / from Sweden / ECHA	PMC and ESTF	Q3 2018
9.	Organise follow-up call to discuss a coordinated approach towards advocacy actions	PMC and ESTF	Sep 2018
10.	Point out the ongoing CLH process for the SCAS to ECHA during the informal discussion following the DD on the EOGRTS TP	PMC	After receiving the DD on the EOGRTS TP