Silver Work Group meeting

Draft minutes, Brussels, 15 March 2018 (13:00-16:00 CET)

Chair: 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 in Annex 1. No remarks / additions; agenda approved.

1.4 Approval of the minutes of the last meetings/calls (19 Oct, 9 Nov, 23 Nov 2017) and status of action points

No remarks / additions; minutes of the meetings of 19 Oct and 23 Nov and of the call of 9 Nov were approved. Tables with the status of the action points from these meetings/calls are available on slides 6-8 in Annex 2. All action points have appropriately been addressed / are ongoing, or will be discussed in this meeting.

1.5 Election new chair / co-chair

Following the PMC and EPMF restructuration, it was proposed to have a chair and co-chair for each WG. Rob Garrett kindly confirmed his willingness to continue supporting the Ag WG but as co-chair instead of as chair. Clémence Siret from SAFT is candidate for the position of Ag WG chair. **The WG approved the appointment of Clémence Siret as chair and Rob Garrett as co-chair of the Ag WG.** This will become effective after the meeting until 2021. The WG thanked Rob Garrett for his continued support.

2 Water Framework Directive (WFD) prioritisation

2.1 Process and timeline

Cf. slides 11-13 in Annex 2. Ag has been shortlisted by JRC as candidate priority substance (PS) (STE-score > 1.8) and JRC drafted an EQS dossier for Ag with a freshwater EQS of 10 ng/L versus our REACH PNEC of 40 ng/L. The revision of the PS list has been postponed (to be in line with the WFD review) and further steps for shortlisted substances as announced in March 2017 by the European Commission (EC) were:

- Confirmation of **PNEC/EQS** in substance-specific sub-groups led by volunteer MS, with the aim of presenting an EQS dossier to the SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) to have a 'harmonised' EQS in the course of 2018 ('harmonised' EQS in this case

refers to an EQS developed within the CIS (Common Implementation Strategy) process, and not set by the EQS Directive).

- Gather further **monitoring data** for Ag in the dissolved fraction (as it was concluded that the dataset for dissolved Ag did not comply with the representativeness criteria - if no further monitoring data received, Ag could be considered a candidate for the Watch List (WL)).
- Re-run STE-score based on confirmed PNEC/EQS and updated monitoring dataset and **conclude on shortlisting** around Oct 2018. MS will be encouraged to take shortlisted substances and their 'harmonised' EQS into account when establishing their 3rd River Basin Management Plan (RBMP).

In the meantime:

- JRC has drafted a WL report. **Ag is not proposed for the WL**. However, judging from certain statements in the report (e.g. Ag being a River Basin Specific Pollutant (RBSP) in 7 MS which 'tends to support the idea of an EU-wide risk'), it seems that JRC still considers Ag a good candidate for prioritisation.
- Additional **monitoring data** for Ag in the dissolved fraction have been gathered, and these data combined with the data previously used in the prioritisation, now fulfil the representativeness criteria. The updated STE-score calculated by JRC is now 1.77 (using PNEC of 10 ng/L), whereas the criterion for shortlisting was STE score > 1.8. At the 26-27 Oct WG Chemicals meeting, PMC asked if - since the updated Ag STE-score is now lower - this means Ag is no longer a candidate for the shortlist. The EC replied that we should wait for the ongoing work on the Ag EQS before concluding whether Ag poses a significant risk at EU level.
- A **silver specific sub-group** was set up in Aug 2017, led by Sweden. Other members are Germany, Latvia, Denmark, France, Eurométaux and PMC. The original aim was to agree on EQSs for all matrices that could be of relevance (incl. sediment) by early 2018, which was very ambitious. Starting point for the EQSs is the JRC silver draft EQS dossier together with available studies from REACH, the RIVM Ag Environmental Risk Limits (ERL) report, the BPR Ag dossier, and the open literature. Discussions are still ongoing (see also next agenda point).
- Both **the EC and the MS** focused on the WL during the 2 previous WG Chemicals meetings and the PS list seems of lower priority. The **timing for the PS is still unclear**. There might be further information on timing at the next WG Chemicals meeting, planned 17-18 April.

2.2 Revision silver PNEC / EQS: update on discussions WG Chemicals Ag sub-group

Cf. slides 14-20 in Annex 2.

Freshwater

- **PMC** has (re-)assessed its dataset, using selection criteria in line with the EQS guidance, MERAG criteria and largely in line with the criteria RIVM used for its Ag ERL report (except for the low DOC, as the Ag specific sub-group agreed that there is currently not enough data available to conclude that DOC influences chronic Ag toxicity). Based on these criteria, some data used for the previous REACH PNEC derivation in 2013 are considered not valid. The report with the updated dataset was circulated to the WG in Dec 2017. An SSD was applied (cf. slide 15 in Annex 2) and using an assessment factor (AF) of 3 (which is the AF used in 2013), this results in a **PNEC of 35 ng/L**. However, the dataset currently does not contain sufficient taxonomic groups to apply an SSD (cf. slide 16 in Annex 2) and therefore, additional tests are proposed (see also next agenda point).

- Since there are currently insufficient taxonomic groups to apply an SSD, **Sweden** is suggesting using the lowest reliable EC_{10} as a basis for the freshwater EQS, which is from the algae test with $AgNO_3$ performed by Fraunhofer for PMC for the SEv (Schlich et al. 2017). They suggest an assessment factor of 10, which would lead to an **EQS of 10 ng/L**. However, they have also conducted an SSD to compare the outcome with the deterministic derivation (cf. slide 17 in Annex 2). Using the highest AF of 5, this also results in an EQS of 10 ng/L.
- PMC has compared both SSD datasets (PMC / Sweden) and while there is agreement on the reliability of most of the studies, there are a number of **discrepancies** between both datasets (cf. slide 18 in Annex 2):
    - Sweden has sometimes used a more conservative approach, using minimum values instead of geometric means if > 1 reliable EC_{10}/NOEC was identified for the same endpoint/species;
    - If there was no EC_{10}/NOEC reported in the study itself, the derivation of the EC_{10}/NOEC was sometimes slightly different;
    - Sweden has rejected a few studies that PMC has accepted.
- There was agreement within the Ag specific sub-group that there are **currently insufficient data to apply an SSD**. Therefore, PMC has indicated they will perform additional tests (see also next agenda point).
- PMC has commented on the discrepancies between both datasets and Sweden will check our comments and take them into account where considered relevant, but if opposite views are identified these will be highlighted for the **SCHEER's consideration**.
- It is noted that even the 10 ng/L PNEC does not result in an **STE-score** for silver > 1.8 with the latest monitoring data. Since 1.8 was the cut-off STE score for the PS shortlist, PMC believes silver should not be on the PS shortlist.
- Further comments/questions:
    - **Geometric means**: 5 of the 13 toxicity values in the PMC dataset are geomeans instead of worst-case values. Two of these geomeans are for waters with different hardness, while the EQS guidance states '*If an effect of test conditions is expected to be the cause of variation in toxicity values (hardness of test water, life stage of the test animal, etc.), averaging of data per species should not be performed*'. The use of these geomeans can therefore be questioned.
    - **Assessment Factor (AF)**: For an SSD approach, the AF can vary from 1 to 5 (AF of 5 is used by default but may be reduced where evidence removes residual uncertainty). Sweden has used the highest AF when deriving an EQS from their SSD but has indicated they are willing to rediscuss when additional data become available. Given the extent and quality of the dataset, but also recognising that there is no mesocosm study, PMC believes an AF of 3 (or maybe even 2?) is realistic. **AP3**
    - The data in the PMC / Sweden datasets are all for **silver nitrate**. The data were not selected on the basis of the test substance but data for other Ag salts were considered unreliable for other criteria (e.g. only nominal values reported, information on physico-chemistry of test medium lacking, …).
    - Sweden has also proposed a **saltwater EQS** and this is based on the same study as the REACH saltwater PNEC (Ward et al. 2006) but a higher AF was used (50 instead of 10)

because no reliable saltwater algae studies are available. PMC will check the marine dataset and suggest additional testing if needed. **AP4**

- It is questioned whether the planned **EOGRTS** and the possibility of a Repr classification can have an impact on the EQS discussions. This could have an impact on the assessment of exposure of man via the environment, but this is not included in the WFD.

- A PNEC < 40 ng/L may have an impact on the Exposure Scenarios (ES). Since the site-specific data used in the ES are quite old, it is suggested to first re-check the exposure data / modelling and recalculate the RCRs. If these are 'high', than a refinement of exposure assessment is proposed. If further refinement is needed, we can look into the development of **bioavailability** models (first step literature search + data-gap analysis, second step to test and build BLM). **AP5-6**

Sediment

Sweden still has not proposed a sediment EQS. As agreed at the last WG meeting, PMC will perform additional tests if our REACH sediment PNEC is challenged. **AP5**

2.3 Additional ecotox testing

Cf. slides 21-22 in Annex 2. At the 12 Jan call, the WG approved the performance of additional tests with *Lemna minor, Anabaena flos-aquae* and *Brachionus calyciflorus* if there were no other reliable data on these species. In the meantime, UBA has confirmed that the data they have are not reliable. Therefore, **the Ag WG formally approved the decision to perform the additional ecotox tests**.

(Post-meeting note: the tests are currently running at Ghent University.)

It is mentioned that for other metals (e.g. Co), there were some issues with the Lemna test and PMC is advised to check if these can be relevant for Ag.

(Post-meeting note: The issues seemed to be related to the fact that a static test was performed and the test concentration over the course of the test could not be maintained. For Ag, a semi-static test (with renewal) will be performed.)

3 Silver reproductive toxicity

3.1 Recap current situation silver reprotox

Cf. slides 25-28 in Annex 2. The scientific data-gap related to reprotoxicity of Ag was addressed in 2015 by submitting a testing proposal (TP) for an **EOGRTS** (Extended One Generation Reproductive Toxicity study) in the silver metal REACH dossier. Since 2015, further research has been published regarding the reproductive toxicity potential of ionic silver (e.g. Sprando et al. 2017 and Babu et al. 2016). Whilst these new studies extend the available dataset, PMC notes that they are impacted by certain deficiencies in experimental design and that they present non-definitive outcomes. As a consequence, PMC's opinion is that 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, but that an update of the TP is necessary. 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.

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 and study start, in particular to evaluate if significant gut microbiome effects could occur at dose levels relevant for the study (see also agenda point 3.5).

3.2 Status EOGRTS Testing Proposal

Cf. slide 29 in Annex 2. The TP is now under evaluation by ECHA and we are waiting for the **Draft Decision (DD)**. France Capon had a meeting with Hannu Braunschweiler from the ECHA Evaluation unit at the day of the present Ag WG meeting and learned that the DD is currently being reviewed by ECHA toxicologists who recognise that our TP is out of date and new data on the reprotoxicity of Ag are available. They have a first assessment of the DD available and were planning to send it to the Lead Registrant early April but since our TP from 2015 is out of date, they would like to have our views on how we see the update of the test design (taking into account the most recent data) before issuing this DD (in other words they will put the DD on hold until they have assessed our updated TP). Only a formally updated TP can be officially taken into account but in the interest of time, they would like to receive asap (i.e. in the next few days) an email confirming that we will update, summarising what we plan to change in the TP and why, and by when we would submit the update.

The update we will do now is an additional opportunity to interact with ECHA. After receiving the DD, we still have the opportunity to have an informal call with ECHA, and we can still submit detailed comments on the DD where we think it is needed. So the current update will increase the chance of acceptance of the TP.

The Ag WG agrees to accept the opportunity to update the TP, and suggests to indicate to ECHA that we need 3 weeks to update the TP. **AP8-9**

Taking into account the evaluation process / timeline, PMC does not expect to initiate the EOGRTS before end 2018.

(Post-meeting note: The updated TP has been submitted on 5 April. ECHA confirmed that they will update the internal DD to take into account the most recent version of the TP. ECHA also indicated that for TP examination decision making, they will anyway always consider dossier updates received within 60 days from sending the DD to the registrant, and they will update the DD before referring it to the MSCA as a next step in the decision-making process.)

3.3 PMC strategy

Cf. slides 30-36 in Annex 2 and Annex 3. The recent recognition of silver as a possible reproductive hazard escalates the already delicate situation regarding Ag regulatory risk / classification. Therefore, PMC has drafted an advocacy strategy.

Comments/questions:

- It is noted that, even if our TP is rejected, the CLH process is the only way to classify a substance.
- Regarding the stakeholders mapping, the WG agreed to wait to contact **Kemi** until we have the DD (**AP10**). For the **ESTF** (European BPR Silver Task Force) contact, it is suggested to identify contacts in their member companies (e.g. Dow, BASF) to try to increase the advocacy efforts of the ESTF (**AP11**). The contact should be initiated ASAP, so we can contact them when we have the DD.

- It is suggested to look into the possibility to differentiate between massive silver and silver powder (e.g. based on bioelution testing) for a potential classification.
- It is noted that the tool to asses the regulatory consequences of a classification, which is under development by Eurométaux, would also be helpful to companies when discussing internally e.g. finances for testing.

3.4 Outcome Tox Expert discussions

Following the last Ag WG meeting, a meeting with Michael Holsapple (expert on DIT) and several Tox Expert discussions have taken place. These are summarised on slides 37-40 in Annex 2. One of the most important outcomes was that **enabling work** is needed prior to the EOGRTS final dose-setting and study start, in particular to evaluate if significant gut microbiome effects could occur at dose levels relevant to the study (see also agenda point 3.5).

Comments/questions:

- It was noted that, when discussing outcomes from reprotox studies, it is important to specify which studies tested nanoAg and which tested soluble Ag compounds.

3.5 Enabling study gut microbiome

Cf. slides 41-45 in Annex 2. The main objective of the study is to investigate the effects of Ag on the (parental) gut microbiome of rats at low dose levels (equivalent to those used in Sprando et al. 2017), and in exposure settings that are relevant and directly comparable to the planned EOGRTS, in order to strengthen our hypothesis that the silver MoA for reproductive effects includes indirect effects via the gut microbiome. A gut microbiome study - in addition to its value for the EOGRTS design / defence - could also provide argumentation pertinent to classification of Ag as reproductive toxicant.

In view of the new information from ECHA, the Ag WG agreed to change position on the gut biome study and initiate the study ASAP. **AP12**

(Post-meeting note: A meeting with Prof. Lison and the Tox Experts took place on 11 Apr.)

Comments/questions:

- It is noted that if the current study shows significant effects of ionic silver on the gut microbiome, this will not be sufficient to conclude that reproductive effects observed in other studies are secondary to biome disturbance, but this will provide some argumentation to support PMC's hypothesis. Showing a causal relation between biome disturbance and reproductive effects is outside the scope of this study, and would require a different study design (e.g. reprotox study with gnotobiotic animals or biome transplantation).

3.6 Status CLH proposals silver active substances (SCAS)

Cf. slide 46 in Annex 2. We are still awaiting the 60-day public commenting period. **AP13**

4 Budget

The **2019 draft budget** is presented on slide 48 in Annex 2. It is noted that the costs related to the EOGRTS have been budgeted already in 2018 and will be largely carried over to 2019.

The budget for potential bioavailability work is not yet included – for discussion at the next WG meeting.

The budget for the biome work is included in the 2018 budget (budget for enabling work included).

5 AOB, next meetings/calls and closing remarks

The next Ag WG meeting is planned on 9, 10 or 11 Oct 2018.

Annexes

1. Agenda & list of participants
2. Slides presented at the meeting
3. Silver strategy (PMC, 1 Mar 2018)

Actions

Table 1. Actions agreed at the 15 March 2018 Ag Work Group meeting in Brussels

	What?	Who?	When?
Water Framework Directive (WFD) silver prioritisation			
1.	Perform additional ecotox tests at Ghent University	PMC Sec	Mar-Jun 2018
2.	Update dataset for SSD with additional ecotox test results and re-derive freshwater PNEC + check criteria to lower the assessment factor (AF)	PMC Sec	After AP1
3.	Discuss test results, impact on SSD and AF with silver sub-group	PMC Sec	After AP1
4.	Check marine dataset for EQS derivation and suggest additional testing if needed	PMC Sec	Mar-May 2018
5.	Re-check the exposure data / modelling and perform a refinement of the exposure	PMC Sec with Ag registrants	Apr-Sep 2018
6.	Discuss need for 2019 bioavailability budget at Oct WG meeting	PMC Sec with Ag WG	Oct 2018
7.	If the REACH $PNEC_{sed}$ is questioned by the silver sub-group, challenge ESTF study (suggest REACH $PNEC_{sed}$ as provisional) and address data gap with well-designed sediment tests (long term, 3 species, natural sediments low in AVS/OC)	PMC Sec	As needed
Silver reproductive toxicity			
8.	Send mail to ECHA to confirm EOGRTS TP update and timing	PMC Sec	ASAP
9.	Update EOGRTS TP and Ag IUCLID file and send to LR for submission	PMC Sec with M Raffray	End Mar - early Apr
10.	Contact Kemi for a meeting to discuss the review of elemental silver	PMC Sec	After receiving DD on EOGRTS TP
11.	Identify contacts within ESTF membership to try to increase the advocacy efforts of the ESTF	Ag WG	ASAP
12.	Organise meeting with prof. Lison on gut microbiome study	PMC Sec with Ag TE	ASAP
13.	Prepare comments on CLH proposals SZ, SCZ and SSZHP taking into account previous comments SZZ + comments recent Sprando et al. study	PMC Sec	During public consultation