Silver Work Group meeting

Draft minutes, Brussels, 19 October 2017 (11:30-16:00 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 meeting (23 March 2017) and status of action points

The minutes of the last meeting were approved. A table with the status of the action points from the last meeting is available on slide 6 in Annex 2.

2 Substance Evaluation (SEv) by Dutch MSCA

2.1 Final results testing and data collection uses nanosilver

The WG was reminded about the content of the final decision and timeline (cf. slide 8 in Annex 2). A summary of the results of the phys-chem characterisation (basic substance properties and dissolution rate testing), the ecotoxicity testing and the use data collection was presented (cf. slides 9-15 in Annex 2). Since the **ecotoxicity tests showed that nanosilver is not more toxic than ionic silver**, PMC concluded that the information in request 2 of the final decision (information on fate of nanosilver in soil) does not need to be provided. **All results were included in the silver REACH registration dossier and submitted by the lead registrant and the 2 nanosilver co-registrants by 13 July**.

2.2 Further process

During a meeting with the eMSCA on 22 May where the results were presented, it was clarified that once the new information is submitted, the **eMSCA has 12 months to evaluate** it (i.e. until 13 July 2018). They can either conclude that no further data is needed and submit a conclusion document to ECHA, or that further info is still needed to address the concern and issue a new draft decision (which may still include the request for information on fate of nanosilver in soil). Once the SEv is finalised, the eMSCA will conclude on how to continue with the concern.

In addition to gathering information on the uses of the two nanosilver forms, a parallel **review of the uses of silver and silver compounds** is ongoing (unrelated to the SEv). A questionnaire will be circulated for this later this year.

Comments/questions:

- What about non-identified manufacturers/users of nanosilver? PMC reached out to the SIEF, but received no additional input from them.

3 Water Framework Directive (WFD) prioritisation

3.1 Status process and timeline

Cf. slides 18-21 in Annex 2. Silver has been shortlisted by JRC as candidate priority substance (STE-score > 1.8) but the prioritisation exercise has been postponed by the European Commission (EC). Further steps for shortlisted substances as announced in March were:

1) 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) early 2018 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).
2) Gather further **monitoring data** for silver in the dissolved fraction (as it was concluded that the dataset for dissolved silver did not comply with the representativeness criteria - if no further monitoring data received, silver could be considered a candidate for the Watch List (WL)).
3) Re-run STE-score based on confirmed PNEC/EQS and updated monitoring dataset and **conclude on shortlisting** around October 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. **Silver is not proposed for the WL**. However, judging from certain statements in the report (e.g. silver 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 silver a good candidate for prioritisation.
- A **silver specific sub-group** has been set up in August, led by Sweden. Other members are Germany, Latvia, Denmark, France, Eurométaux and PMC. A first conference call was held 5 Sep and a second call is planned 20 Oct. Sweden would like to agree on EQSs for all matrices that could be of relevance (incl. sediment) before end 2017, which is very ambitious. Starting point is the JRC silver draft factsheet, which suggests a freshwater PNEC of 10 ng/L (versus REACH freshwater PNEC of 40 ng/L). The group is compiling a list of available studies, shared through an online platform. At the same time, PMC is (re-)assessing its ecotox dataset.

  (Post-meeting note: The second call of the silver sub-group has been postponed to 6 Nov.)
- Additional **monitoring data** for silver 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 with their proposed PNEC of 10 ng/L) is now 1.77. Only aggregated data (not the raw data) are shared with PMC.

  (Post-meeting note: The criterion for shortlisting was STE score > 1.8. At the 26-27 Oct WG Chemicals meeting, PMC asked if - since the updated silver STE-score is now lower than 1.8 - this means silver is no longer a candidate for the shortlist? The EC replied that we should wait for the ongoing work on the silver EQS before concluding.)

It is concerning that above work is continuing, while a clear timeline and clear legislative process from the EC is still lacking. Furthermore, the silver-specific sub-group was set up with almost 6 months delay, which leaves very little time to conduct the work needed. In addition, it is unclear how the recent call for tenders to derive EQS launched by the EC is linked to the ongoing work. **PMC will send a letter to the EC requesting further clarity on process and timing**.

(Post-meeting notes:

- *PMC sent a letter to the EC on 20 Oct. Our request for more clarity was reiterated by Eurométaux.*
- *At the 26-27 Oct WG Chemicals meeting, the EC explained that it was not in the position to give a definitive timeline on the next steps in the process because there is still a lot of uncertainty on some aspects that can influence the timeline and future decisions. They will provide further information at the next WG Chemicals meeting (Jan 2018 - tbc). A revision of the EQS Directive is not foreseen by the EC in 'the short-term' and any decision on the next steps will be made only after the conclusion of the upcoming Evaluation of the WFD. The EC is still considering how to address the shortlisted substances from the PS review, in the absence of an immediate proposal to revise the PS list.)*

3.2 Status revision silver PNEC / EQS

Freshwater

Cf. slides 22-24 in Annex 2.

- **Sweden** is questioning whether there are data from enough taxonomic groups to apply an SSD, and is currently suggesting using the lowest reliable EC_{10} as a basis for the freshwater EQS, which is from the algae test with silver nitrate performed by Fraunhofer for PMC for the SEv (Schlich et al. 2017). They seem to be suggesting an assessment factor of 10, which would lead to an EQS of 10 ng/L.
- **PMC** is currently (re-)assessing its dataset, using selection criteria in line with MERAG criteria and largely in line with the criteria RIVM used for their report on Environmental Risk Limits (ERL) for silver (cf. slide 23 in Annex 2). Based on these criteria, some data used for the previous REACH PNEC derivation in 2013 are considered not valid. However, taking into account also recent published data, PMC believes there are still data from sufficient taxonomic groups to apply an SSD. The PMC re-assessment should be available for internal review by early Nov. **AP1-2**
- Comments Ag WG:
  - It is suggested to also look at the silver ERVs for classification purposes, and to advance the work on bioavailability for silver. **AP3**
  - If there are data on only a few species missing to apply a SSD, **the WG would be prepared to generate these data / perform additional studies to strengthen our SSD approach** (to be further discussed once the assessment is available).

Sediment

Cf. slides 25-30 in Annex 2 and the expert opinion in Annex 3. Sweden has not proposed a sediment EQS yet but they have indicated they would look at both REACH and BPR sediment data. PMC checked the silver sediment PNEC derivation of different stakeholders (PMC, ESTF, UK EA) based on

information available in the public domain and/or information from newly generated toxicity data. As explained on slides 26-28, none of these PNEC derivations is robust. Since Sweden is the rapporteur MS for the SCAS (Silver Containing Active Substances) under the BPR, it is expected that they will propose the (overly conservative) ESTF sediment PNEC, which would result in RCRs >> 1 in the REACH exposure scenarios. If this is the case, PMC has a number of options as outlined on slide 30 in Annex 2. These options were discussed with the PMC Ag EQS sub-assembly during a call on 12 Oct, and they recommended option 4 (address data gap with well-designed sediment tests), since this is the only scientifically robust option. The Ag WG agrees to performing additional tests if our REACH sediment PNEC is challenged, but would like to reword the PMC action to '**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)**'. **AP4**

4 CLH proposals silver containing active substances (SCAS)

4.1 Proposed CLH for silver zeolite (SZ), silver copper zeolite (SCZ), silver sodium zirconium hydrogen phosphate (SSZHP)

Cf. slides 33-34 in Annex 2.

- 3 further CLH proposals were submitted by Kemi (Sweden) for SCAS under the BPR. For SZ and SCZ a **Repr 2 classification** is proposed and for all 3 SCAS an **environmental classification** (Aq acute 1 & Aq chronic 1) is proposed. The proposed human health classifications are favourable to the original proposed classification of SZZ and the achieved result seems largely carried over. For the environmental classifications however, the same error has been made as for SZZ not fully recognizing the metals classification scheme.
- It is expected that the 45-day public commenting period will start soon.

4.2 PMC commenting

Cf. slide 35 in Annex 2.

- PMC is planning to submit comments on the **Repr classifications** (re-iteration earlier PMC comments SZZ + specific comments on recent Sprando et al. study as outlined in Annex 4.1 + link to EOGRTS TP to address data gap) and on the **environmental classifications** (re-iteration earlier PMC comments SZZ). **AP5**
- The importance of re-iterating our previous comments on **argyria** is stressed. At the RAC meeting where the SZZ CLH was discussed, RAC did not consider the argyria reported for SZZ to be of toxicological significance (and hence did not accord STOT-RE classification for this effect). However, the latest Kemi CLH proposals seem to come back to this (e.g. in the SZ CLH dossier, it is stated that a parental NOAEL cannot be set in the Sprando et al. study due to tissue pigmentation). Independent of any reproductive toxicity considerations for ionic silver, a change of regulatory mindset about the structural and functional significance of argyria (i.e. regarding its adversity) would have broad impact.
- **ESTF** indicated that they have not yet decided whether they will submit comments during the public commenting period (to be discussed at the 24 Oct meeting with their members). In any case, they will not fight the read-across / applicability of the (most adverse) 2-gen SZZ study to other SCAS which contain zeolites as this would lead to a data gap. ESTF also indicated that they included the Sprando et al. study in the BPR dossier on request of Kemi.

- EPMF was approached by a member-company of the ESTF who is in the process of preparing a BPR dossier for elemental silver and who requested **data-sharing** / wants to include REACH data in their dossier. They sent a request to Kemi to consider these data and Kemi indicated they have not started their review of elemental silver yet, and that in principle they would be prepared to look at new data, but that these would have to be submitted via the ESTF. Kemi therefore suggested that they would first check if there are any data gaps that could be filled using REACH data.
- PMC thinks it would be a good idea to convene another meeting with Kemi once they have started the review of elemental silver (early 2018?), to give an overview of the data in the silver REACH registration dossier, and to state that SCAS which contain zeolites are very different from elemental silver. **The Ag WG agrees to explore the possibility for another meeting with Kemi early 2018.** **AP6**

5 Testing proposal EOGRTS

The public consultation on our EOGRTS TP on silver acetate started 27 Sep. Only third parties (not directly involved in the dossier) can send comments until 13 Nov 2017. After that, a scientific and legal evaluation will be done, a draft decision will be prepared and sent to the registrant (so far only to the LR) and a commenting period of 30 days will then start. A final decision will be prepared on that basis and communicated to the registrant. This timeline means that the testing could start in 2018.

5.1 Status current knowledge silver reprotox

Cf. slide 39-53 in Annex 2 presented by M. Raffray and Annex 4.1-4.2. Over the last 2 years, the overall balance of evidence on silver reprotox shifted adversely. In particular, there are 2 recent studies which are of concern:

- **Sprando et al. 2017**: US FDA OGRTS on silver acetate; Klimisch 2 study showing developmental tox and effects on fertility. This study was used by Kemi in their recent SCAS CLH proposals. We however disagree with Kemi's assessment of the study's severity outcome (fertility endpoint). Moreover, the study does not inform on the mode of action (MoA) and possible secondary effects and shows several shortcomings compared to the EOGRTS design. Nevertheless, if replicated, the developmental tox and fertility effects would trigger extension of the EOGRTS to the F2 generation (1B cohort).
- **Babu et al. 2016**: linked to above study but more specifically looking at immune parameters in the offspring (long-term DIT work) and showing immunotoxicity. This study was not used by Kemi, which is surprising, but EFSA considers it an important study (**AP7**). It is however not as powerful as an EOGRTS DIT assessment but could impact the DIT weight-of-evidence position in our TP (cf. also agenda point 5.2).

Given the recent developments, the fear is that silver is on a trajectory for **Repr classification** and that we are not allowed to perform the EOGRTS. It is recommended to aim for a defence-in-depth, i.e. try to avoid a Repr classification altogether, but the fall-back option is Repr Cat. 2 (which is still better than Repr Cat. 1B), whilst also defending the TP justification for an EOGRTS.

Comments/questions:

- It is noted that EFSA published in 2016 the re-evaluation of silver (E 174) as food additive. The Panel concluded that the information available was insufficient to assess the safety / conduct a

risk assessment of silver as food additive (lack of tox studies, characterisation and release data) and recommended that additional data in line with the current Guidance document on evaluation of food additives would be required. The Panel did not identify major criticisms of Babu et al.

- The PMC secretariat is reminded of the need to conduct the silver human health literature reviews more regularly to ensure we do not miss important publications. **AP8**
- It is noted that nanosilver reprotox studies are also troubling but these studies are mostly flawed *(in vitro* studies, no standard study designs etc.).

5.2 Need for revision TP / enabling studies

Since our TP is now out of date, we have no option but to re-consider it. The current version includes the basic design (no cohorts) but the WG already recognised that our position on the DNT cohort was borderline. It looks like we now have to assume the most complex study design (inclusion of all cohorts). Moreover, a more robust EOGRTS design is needed in terms of parameters examined / coverage of indirect effects.

Suggestions for revision of the TP / enabling work include:

1) Design study to try to prove that Ag reprotox is a secondary effect (look at stress hormones in adults and neonates and look at gut microbiota);
2) Design study to try to prove that MoA is of no / limited relevance to humans;
3) Design study to try to prove that silver reprotox is confined to exposure levels significantly above those relevant to human risk assessment.
4) DIT enabling work

In addition to M. Raffray's assessment of the recent studies and their impact on our TP, PMC also asked a DIT expert (Michael Holsapple) for a more detailed review of the DIT findings (cf. slides 54-56 in Annex 2 and Annex 4.3). Both reviews were largely in agreement and M. Holsapple confirmed that the Babu et al. study shows a number of weaknesses compared to an EOGRTS but it does provide suggestive evidence for the possibility that silver exposure can cause DIT, which is a sufficient trigger for **inclusion of the DIT cohort** in our EOGRTS. In addition, he recommended to include **distributional analysis** in our TP, check the **possibility of indirect effects** and revise the dose-levels in our TP.

Comments/questions:

- It was noted that epidemiology studies in humans supplied to RAC have been ignored in the past.
- For the complex EOGRTS design, we should assume a cost of 1.25 to 1.5 million €:
  - EOGRTS incl. 3 cohorts (F2 generation + DNT + DIT): 600-900 k€
  - Toxicokinetics (TK): ± 70 k€
  - Dose/formulation support: ≥ 40 k€
  - Enabling work: ± 150 k€
  - Study monitoring costs, consultancy / design costs and contingency need to be added to above amounts
- Although the Babu et al. study did not show silver induced thymic effects, the recent SCAS CLH proposals do include studies showing some effects on the thymus. It is noted that M. Holsapple did not review the CLH proposals.
- **Dosing revision**: TP dose levels are too high now and might induce indirect effects (stress, gut microbiota impacts); suggestion to reduce to levels that will not cause secondary effects but that

are not so low that it is no longer relevant to humans. However, this is technically difficult to design.

- **Timing**: it is expected that we will receive **the draft decision** on our TP in January. We could start the enabling work before receiving the draft decision (would include *in vivo* work but unless it is the study for the actual REACH endpoint, you can perform other studies, e.g. TK study with additional parameters) or we could argument why further enabling work would need to be done in our comments to the draft decision. We may have results in 4-5 months so this will likely be too late to use them in our comments to the draft decision. On the other hand, you need to have information on secondary effects to prove your point.
- **The WG agrees that:**
  - **a thorough technical discussion between the WG company toxicologists, M. Raffray and M. Holsapple is needed ASAP on the feasibility of enabling work and how to revise our TP (AP8);**
  - **a recommendation to the Management Committee should be made soon after that (start enabling work now or wait), followed by a decision (AP10-11);**
- It is suggested to check the possibility to **withdraw our TP** based on new evidence, since the TP was drafted in 2015 and is now considered out of date. **AP12**

  (Post-meeting note: Eurométaux confirmed that it is impossible at this stage to withdraw and re-submit our TP. The process can only be influenced via the consultation on the draft decision (informal call with ECHA + written comments) and worst case via an appeal (we have 3 months after receiving the final decision).)
- It is suggested to try to convince ESTF of the defence imperatives arising from the possibility that Repr Cat. 2 classification becomes Cat. 1B. **AP13**

6 Workplan and budget

The current **2017 expenses** are presented on slide 59 in Annex 2. It is expected that the end-of-year expenses will be under budget mainly because the costs for the SEv were approximately 280 k€ less than budgeted (the soil fate testing was not needed and the ecotox testing and use update costed less than budgeted).

The **2018 draft budget** is presented on slide 60 in Annex 2. There have been a few changes to the budget since the March Ag WG meeting:

- The 2018 **SEv** budget for the 2nd tier (soil fate testing) was removed since the 1st tier was sufficient and the dossier has been updated/submitted by July 2017. In case the eMSCA decides the soil fate testing is still needed, the budget is available in the reserves.
- The 2018 **EOGRTS** budget previously included 2 EOGRTS (bulk and nano silver) as recommended by the WG (a TP for the bulk form was submitted but the Ag WG agreed during its Oct 2016 meeting that there may be a risk we have to test nanosilver as well and suggested to budget accordingly) but the PMC Secretariat questioned the relevancy to have these budgets both available in 2018. Based on internal discussions but also with Eurométaux experts, it is unlikely that both studies will have to be conducted in parallel, as it is questionable that ECHA would accept two animal tests at the same time on the 'same substance' (cf. slide 61 in Annex 2). Therefore, the PMC Management Committee recommended to remove the budget for the EOGRTS on nanosilver from the 2018 budget. The Ag WG agrees to remove this for 2018 but does not necessarily agree that both tests would be on the

'same substance', as the test substance in the TP is silver acetate, whereas the test with the nanoform would be performed with nanosilver. Furthermore, it is difficult to compare the 2 tests, as the human health datasets for ionic silver and nanosilver are very different, and the additional preparatory work would also be different (e.g. the gut microbiota seems less affected by nanosilver, meaning additional work on this area would be needed).

Further suggested changes to the 2018 budget (AP14) are:

- The Ag WG agrees to add 150 k€ for the additional sediment tests (cf. agenda point 3.2).
- The Ag WG agrees to budget 1.5 million € for the EOGRTS (full test design including F2 generation, DIT and DNT cohorts, TK, dose/formulation support, enabling studies, study design/monitoring).

7 AOB, next meetings/calls and closing remarks

- The amendments of the REACH Annexes to address nanoforms are currently open for feedback until 6 November. PMC will comment through Eurométaux.
- GHS nano – different classification for different physical forms; we will rely on comments Eurométaux.
- **The next Ag WG meetings are planned 15 March 2018 and 9, 10 or 11 Oct 2018.**

Annexes

1. Agenda & list of participants
2. Slides presented at the meeting
3. Background document 'Expert opinion on the derivation of a PNEC silver for freshwater sediments' (ARCHE, 15 Sep 2017)
4. Background documents on silver reprotox:
   - 4.1. 'SCAS CLH dossier reviews / Sprando et al. (2017) review / Updated Ag literature search' (M. Raffray, 31 Aug 2017)
   - 4.2. 'New developmental immunotoxicity evidence from Babu et al. (2016) study' (M. Raffray, 5 Sep 2017)
   - 4.3. 'Assessment of Developmental Immunotoxicity Studies for Silver' + background documents (M. Holsapple, 17 Oct 2017)

Actions

Table 1. Actions agreed at the 19 October 2017 Ag Work Group meeting in Brussels

	What?	Who?	When?
Water Framework Directive (WFD) prioritisation			
1.	Circulate assessment Ag chronic freshwater dataset + updated PNEC derivation	PMC Sec	Early Nov
2.	Organise call Ag WG to discuss updated PNEC derivation	PMC Sec	Mid/End Nov
3.	Check Ag ERVs for classification purposes, and consider costs/timelines of further work on Ag bioavailability	PMC Sec	2018
4.	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

CLH proposal silver containing active substances (SCAS)			
5.	Prepare comments on CLH proposals SZ, SCZ and SSZHP taking into account previous comments SZZ + comments recent Sprando et al. study (cf. Annex 4.1)	PMC Sec	During public consultation
6.	Contact Kemi for a meeting early 2018 to discuss the review of elemental silver	PMC Sec	End 2017
Testing proposal EOGRTS			
7.	Check EFSA position on Babu et al. 2016 study	N. Rajapakse	ASAP
8.	Perform silver human health literature reviews more regularly to ensure we do not miss important publications	PMC Sec	ASAP
9.	Expert technical discussion on the feasibility of enabling work and how to revise our TP	M. Holsapple + M. Raffray + Ag WG company toxicologists	F2F meeting 23 Nov
10.	Recommendation to the PMC Mgmt Cttee on enabling work for our TP (start now or wait)	Ag WG	After AP8
11.	Decision on enabling work for our TP	PMC Mgmt Cttee	After AP9
12.	Check possibility to withdraw our TP with Eurométaux / informally with ECHA	PMC Sec	ASAP
13.	Try to convince ESTF of the defence imperatives arising from the possibility that Repr Cat. 2 classification becomes Cat. 1B	PMC Sec	ASAP
2018 budget			
14.	Add 150 k€ for the additional sediment tests and budget 1.5 million € for the EOGRTS	PMC Sec	ASAP