European Precious Metals Federation

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Silver Work Group Meeting

2 April 2019 | Brussels, Belgium

European Precious Metals Federation

Welcome & Introduction

Confidentiality and Competition law

Tour-de-table and apologies

DO	DON'T
Application of competition law	
Art. 101 and 102 TFEU may be applicable to the conclusion of any preliminary agreement and activities of any preliminary phase.	Don't assume that conflicts with competition law are excluded simply by the fact that the Association's Articles of Association and Internal Rules complies with the provisions of the REACH Regulation.
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Involve a Trustee for the exchange of Confidential Information.	The exchange of Information concerning market behaviour and having the object or the effect of preventing, restricting and/or distorting competition is inadmissible; in particular, this relates to: - Production capacities; - Productions or sales volumes; - Import volumes; - Market shares; - Price policy; - Distribution and marketing terms; - Marketing strategies; - Information regarding the relationship with suppliers.
Documentation on Cooperation	
Keep minutes of all meetings which detail the subject of the meeting. In case of uncertainty, have the contents of the minutes reviewed by an external legal expert prior to sending them to all Members. Stop all meetings which are not in compliance with these Guidelines until a legal expert has been involved.	

Approval of the agenda

1. Welcome and Introduction *(09.00 – 09.15)*
2. WFD prioritisation brief update *(09.15 – 09.30)*
3. Second MISA Workshop: key conclusions/learnings *(09.30 – 09.45)*
4. Silver reproductive toxicity *(09.45 – 11.00)*
   - Recap situation silver reprotox
   - EOGRTS TP: timeline, DD and comments
   - Enabling study gut microbiome: results

Coffee break (10.30 – 10.45)

   - Science strategy: Ag read-across, TK work, preparation EOGRTS
5. CLH proposal silver nitrate *(11.00 – 11.20)*
6. Advocacy strategy silver reprotox *(11.20 – 11.50)*
7. Inclusion of silver acetate in the EPMF portfolio *(11.50 – 12.05)*
8. Workplan and budget 2020 *(12.05 – 12.20)*
9. AOB, next meetings/calls and closing remarks *(12.20 – 12.30)*
   - LR changes due to Brexit

added

Lunch (12.30 – 13.30)

FOR APPROVAL

Approval of the minutes of the last meeting (10 Oct. 2018)

Final draft minutes of the meeting on 10 October 2018, circulated on 26 October 2018

APPROVAL OF DRAFT MINUTES

Status action points last meeting (1/2)

	What?	Who?	Status
Water Framework Directive (WFD) prioritisation			
1	Include rapid removal concept in workplan MISA Environment for Ag + include in Ag dossiers	EPMF Sec	**ONGOING**
2	Comment on revised EQS dossier Sweden / participate in Ag sub-group discussions	EPMF Sec	**DONE**
3	Request offers for well-designed sediment tests for derivation $PNEC_{sed}$ (long term, 3 species, natural sediments low in AVS/OC)	EPMF Sec	**TO DO**
4	Update strategy doc Ag EQS with input Ag WG meeting (replace UK by Belgium as key ally MS)	EPMF Sec	**DONE**
5	Publish results additional freshwater ecotox tests and impact on SSD in peer-reviewed scientific journal	EPMF Sec	**ONGOING**
6	Include results Ag ecotox tests + updated SSD + updated ERVs in Ag dossiers	EPMF Sec	**ONGOING**
7	Re-check the exposure data / modelling and re-calculate RCRs	EPMF Sec with Ag registrants	**TO DO**
8	Literature study on mitigating parameters affecting chronic tox of Ag towards freshwater organisms	EPMF Sec	**ONGOING**
9	Initiate contacts / organise meetings with key MS for advocacy	EPMF Sec + national industry organisations	**ONGOING**
10	Check marine dataset for EQS derivation and suggest additional testing if needed	EPMF Sec	**TO DO**

Status action points last meeting (2/2)

	What?	Who?	Status
Silver reproductive toxicity			
11	Inform the Ag WG on timeline for the SCAS	EPMF Sec	**Cf. Agenda point 5**
12	Follow-up request joint meeting EPMF/ESTF/ECHA/KemI	EPMF Sec	**DONE**
13	TK data mining on major Ag reference substances in support of an improved read-across approach	EPMF Sec	**DONE**
14	Organise meeting EPMF/ESTF TE to discuss read-across testing strategy	EPMF Sec	**DONE**
15	Initiate bio-elution testing once testing strategy agreed	EPMF Sec	**NOT DONE (cf. Agenda point 4)**
16	Include suggested tiered approach to improve read-across in EPMF's MISA HH workplan	EPMF Sec	**DONE**
17	Update strategy doc Ag reprotox with input Ag WG meeting	EPMF Sec	**DONE**
18	Ask ECHA to involve European Commission (DG ENV + DG Growth + DG SANCO) in joint meeting EPMF/ESTF/ECHA/KemI	EPMF Sec	**DONE**
19	Prepare comments on CLH proposals SZ, SCZ and SSZHP taking into account previous comments SZZ + comments recent Sprando et al. study	EPMF Sec	**During public consultation**
2019 Budget			
20	Include an additional 250 k€ for the further testing to improve our read-across approach (under dossier maintenance, split 50/50 over Ag metal/Ag compounds)	EPMF Sec	**DONE**

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Water Framework Directive (WFD) prioritisation : brief update

WFD: Brief update – Reminder process

- Monitoring based exercise JRC: Ag shortlisted as potential PS (STE score > 1.8)
- First draft **EQS dossier**: freshwater EQS of 10 ng/L proposed (REACH PNEC = 40 ng/L)
- European Commission proposed **process** for PS shortlist:

PNEC	• To be discussed in substance-specific sub-groups • Ag group: **SE** (lead), DE, DK, FR, LV, EM & EPMF	…on hold…
Ag monitoring data	• MS to send further Ag monitoring data	done
STE score	• Re-run STE-score & conclude on shortlisting	STE < 1.8
Output	• EQSs harmonised at EU-level → MS encouraged to take into account shortlisted substances for 3rd RBMP	

- Current timing for PS: after WFD fitness check (end 2019?)

WFD: Brief update – Ag sub-group

- **Sweden** sent revised Ag EQS dossier to Ag sub-group 18 Oct 2018:
  - takes into account EPMF test data but disregards other literature data that were previously considered reliable ▶ freshwater chronic EQS of 10 ng/L
  - 1 week for providing written comments
  - EPMF provided comments on revised dossier, defending again the EQS value of 42 ng/L, comments forwarded to the Commission
  - Germany commented that the Sweden proposed EQS is 'plausible'

- **Ag EQS setting in Sweden postponed**:
  - reviewers unable to assess all data since part not public yet
  - impact assessment on silver inadequate
  - warranted to await revision WFD / investigation of Ag as PS
  - Withdrawal Fisheries and Mussel Regulation (2001: 554) not sufficient reason for introducing the proposed value for Ag in HVMFS 2013:19

- Currently **no lead of Ag sub-group** ▶ action European Commission

WFD: Brief update – Follow-up actions EPMF

- **Comments** provided on revised EQS dossier from Sweden ▶ will be sent to next lead once identified
- **Belgium** contacted as possible new lead ▶ no expertise / time to get involved
- **Publication** revised freshwater EQS ongoing
- **Platform presentation** on revised freshwater EQS at SETAC Annual Meeting in Helsinki (26-30 May) accepted
- Inclusion results Ag ecotox tests + updated SSD + updated ERVs in **Ag dossiers** ongoing
- **Bioavailability**: offer on review of bioavailability effects on chronic Ag toxicity to aquatic organisms under review
- **Sediment tests**: offers labs still to be requested

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Second MISA Workshop : Key conclusions / learnings

Key conclusions (1/2)

- Good IND participation to MISA:
  - 18 consortia
  - 321 substances

- ECHA positive on MISA (organisation, participation and IND engagement)

- ECHA positive on quality EPMF HH workplan

- Non-MISA participation metals in focus of ECHA / MS

  → serious requests for additional testing & dossier revisions

Key conclusions (2/2)

- 2nd MISA workshop 7 Feb in Helsinki (ECHA premises)
- Focus on **environmental** endpoints
  - IND to complete Self-Assessment Tool
  - 4 topics identified by EM and ECHA:
    - Read-across
    - ERV/PNEC derivation
    - Bioaccumulation and Secondary Poisoning
    - Difficult-to-test substances.
- 3 EPMF presentations:
  - BAF and BCF for data-poor metals
  - ERV/PNEC derivation for data-poor metals
  - QICARs for data-poor metals (*project under ETAP*)
- 25 key learnings drafted by EM / ECHA + meeting minutes

MISA Workplan ENV

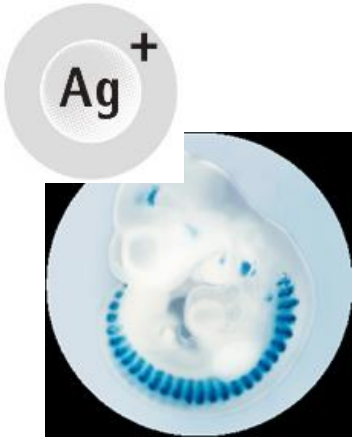
- EPMF workplan drafted & shared with membership 1 March
  → no input received
  → submitted to ECHA 18 March (<29 March deadline)
- Key actions identified (relevant to Ag):
  - Drafting RAJR (read-across justification reports) + addressing counter-ion effect (*addressed under ETAP*)
  - Proper documentation TDp in dossier
  - Update and refine PNEC/ERV
- Actions partly covered in 2019 budget or included in draft 2020 budget

Silver reproductive toxicity

Recap situation silver reprotox

EPMF response

- EPMF original TP EOGRTS in 2015
- Update Apr 2018 (highlights data gaps / improved design need)
- TP accepted in DD …*slides follow*…
- Other science, e.g. is indirect toxicity influential? …*slides follow*…
- **Strategy layered ▶ goal is accurate hazard assessment but avoiding Cat. 1B if at all possible**



SCAS classification (KemI / RAC)

- SZZ: Repr Cat. 1B proposed, Cat. 2 agreed; RAC attribute effects to Ag^+
- SZ & SCZ: Repr Cat. 2 proposed (no RAC decision yet)
- $AgNO_3$: Repr Cat. 1B proposed …*slides follow*…
- Ag: KemI intent to propose Cat 1B!!
- **Repro Cat 1B problematic for biocidal & general Ag sectors**

Latest news (cover every angle…)

- Information sharing with ESTF
- Intelligence on regulator intent re SCAS (e.g. CLH plans)
- Identify any key weakness in industry dataset on Ag…*slides follow*…
- **Work needed on dataset robustness / leverage both sectors**

Latest data (US FDA studies)

- New reprotox data on ionic Ag after SCAS 2-gen reprotox studies
- Sprando & Babu studies – apparently confirm devtox, plus also fertility and developmental immune effects Ag^+
- **Credible originators <u>but</u> flaws in studies/uncertainties ▶ EPMF analysis / expert input**

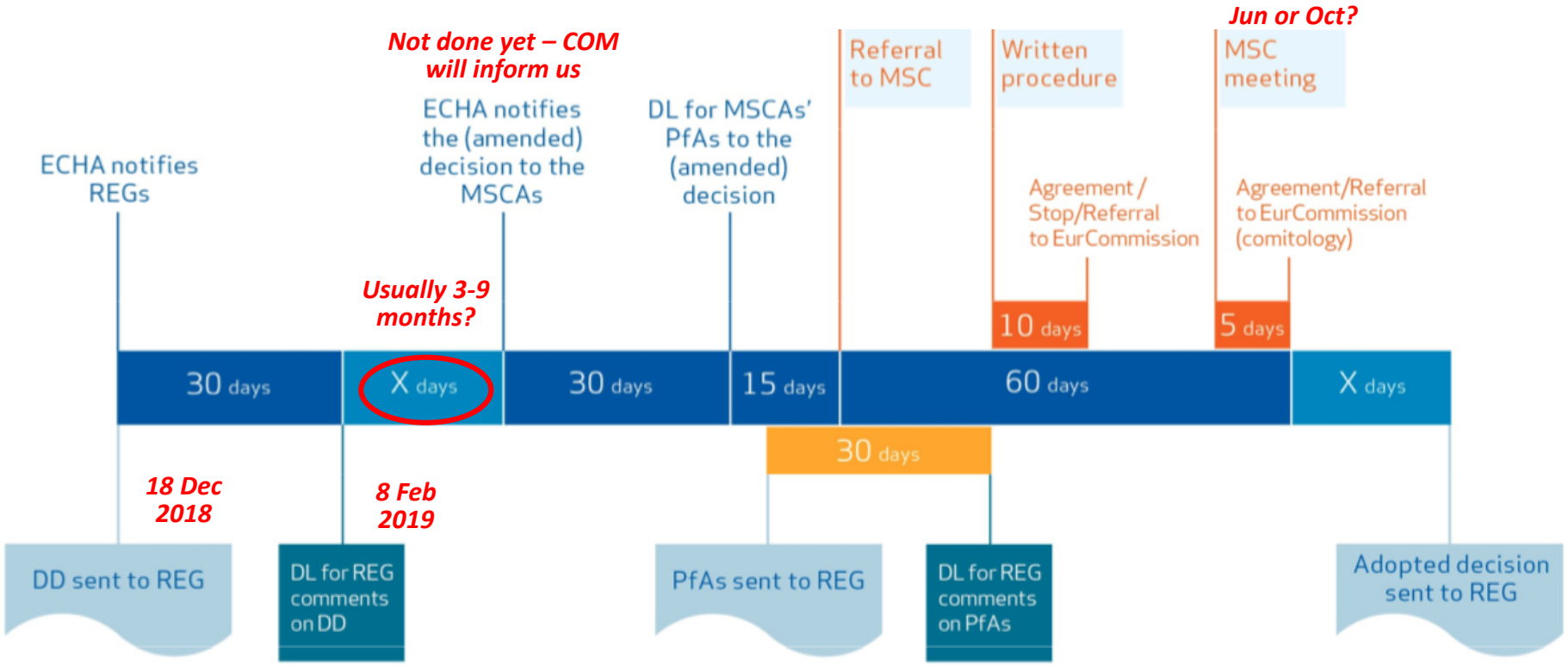
Reminder: respective industry sector subsets

Scope of REACH Ag Dossiers vs Ag Biocide Dossiers

	Ag REACH	Ag BPR
Scope	**EPMF** Ag project includes 8 substances/Dossiers: **1. Silver** (incl. nano) 2. Disilver oxide **3. Silver nitrate** 4. Disilver sulphate 5. Disilver carbonate **6. Silver chloride** 7. Silver bromide 8. Silver iodide	**ESTF** single core active substance dossier supporting 10 substances ('SCAS'): **1. Silver** 2. Silver (reaction mass with SiO2) (nano) **3. Silver chloride** 4. Silver chloride (reaction mass with TiO2) **5. Silver nitrate** * 6. Silver sodium hydrogen zirconium phosphate * 7. Silver phosphate glass 8. Silver zeolite * 9. Silver zinc zeolite * 10.Silver copper zeolite *
Under review by	ECHA (Dossier Evaluation)	KemI, Swedish CA
CLH	Not a requirement	Requirement (* = CLH proposal submitted; * = CLH opinion adopted)

Regulatory decisions have shared relevance under both regulations!

EOGRTS TP: process and timeline



NB: A decision can be adopted directly if no PfAs are received.

- Final decision expected between Jun 2019 and Feb 2020
- EOGRTS test results not available before **mid-2021 at the earliest**

EOGRTS TP: Draft Decision (DD) 18 Dec 2018 (1/2)

- **TP accepted**
- EOGRTS (Annex X, Section 8.7.3.; test method: OECD TG 443) in **rats**, **oral route** with the analogue substance **silver acetate** (EC number 209-254-9; CAS number 563-63-3):
  - **Ten weeks premating exposure duration** for the parental (P0) generation;
  - Dose level setting shall aim to induce systemic tox at the highest dose level;
  - Cohort 1A (Repr tox);
  - Cohort 1B (Repr tox) **without extension** to mate the Cohort 1B animals to produce the **F2 generation**; and
  - Cohort 3 (**Developmental immunotoxicity**)
- **Test design / test article as proposed**
- Deadline to comment: 8 Feb 2019
- (Deadline for dossier update: 11 Mar 2019)
- **24 months** after the final decision to submit the EOGRTS test results

EOGRTS TP: Draft Decision (DD) 18 Dec 2018 (2/2)

- **Test substance / grouping and read-across hypothesis**
  - ECHA agrees to use of **silver acetate** as test material to address potential toxicity due to free silver ions
  - **Read-across approach** *'considered **plausible** for the purpose of the testing proposal evaluation'*
  - Final determination on the validity of the read-across approach premature ▶ *'eventual validity of the read-across hypothesis and grouping approach will be reassessed once the requested information is submitted'*

- **Dose-level setting** will be determined based on ancillary / DRF studies, also incorporating TK endpoints
  - ECHA: *'highest dose level shall aim to induce **systemic toxicity**, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.'*
  - If no relevant data for dose level setting ▶ report results **DRF** with main study to support justifications of dose level selections and interpretation of results

EOGRTS TP: Comments DD

- DD discussed at **Ag Tox Experts meeting 19 Dec**
  - No technical comments on DD ▶ no need for TP related dossier update
  - Comment on **timing** given complexity of EOGRTS / prep work + limited number / availability of labs able to perform test
  - Continue work on strengthening grouping and **read-across** approach (additional *in vivo* TK testing)
  - **Dose-level setting** ▶ await results AgAc biome study (but also need to factor in TK considerations – cf. above)

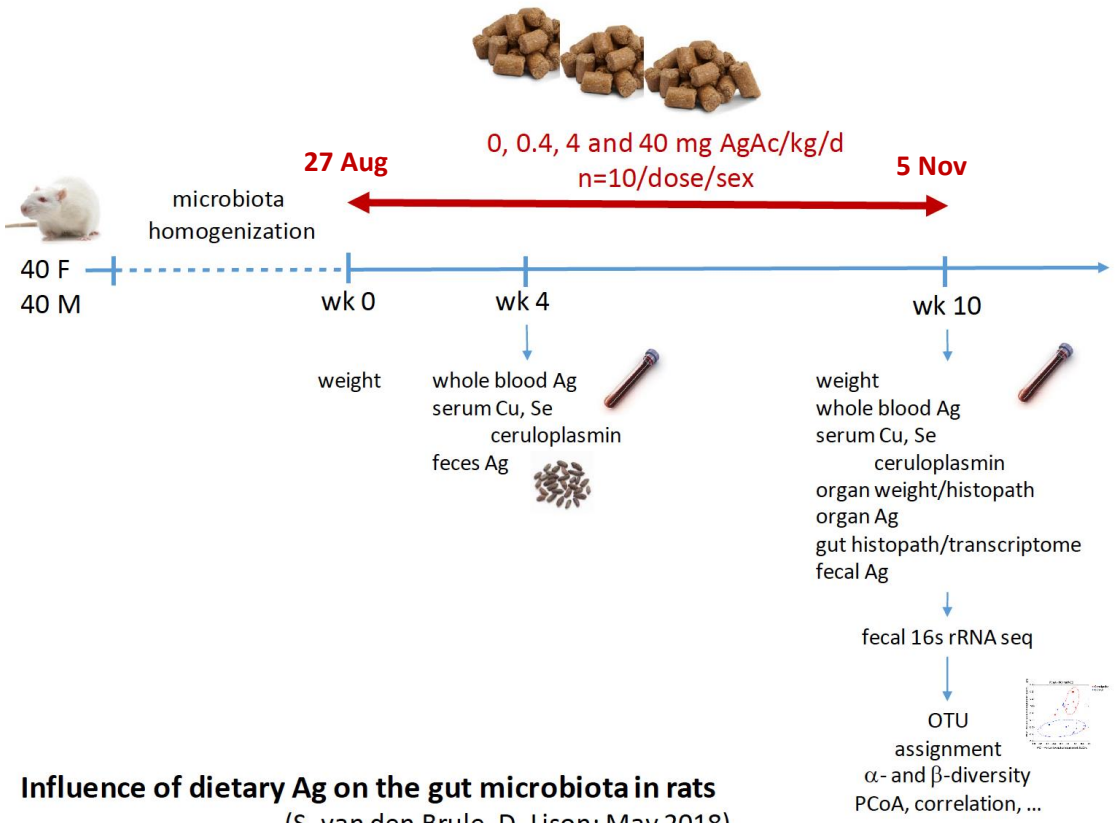
- EPMF contacted **4 CROs** on timing / availability EOGRTS ▶ request extension of timing from 24 to **36 months**

- Comments + lab statements submitted by **8 Feb deadline**

- Draft offers from CROs in line with EPMF **budget** for EOGRTS

Enabling study gut microbiome: reminder study aim

EPMF sponsored support study: Effects of Ag on gut microbial populations / influence re indirect toxicity



Influence of dietary Ag on the gut microbiota in rats
(S. van den Brule, D. Lison; May 2018)

- Study at Louvain University
- Ag^+ biocidal activity may cause indirect toxicity/ stress ▶ dysbiosis ▶ repro effects
- Data (rat model) at low dose Ag^+ exposures was unavailable
- Helps interpretation of (adverse) Sprando / Babu studies
- Supports dose-level setting for EOGRTS
- Fallback use: may mitigate re Cat 1B
- Includes useful supplementary studies regarding MoA (Cu, Se Cp)

Enabling study gut microbiome: results (1/6)

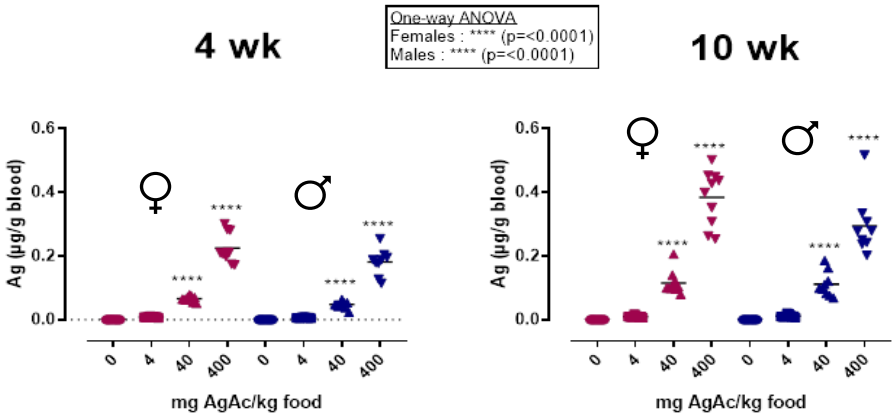
- 2 **mortalities** during study (♂ - MD & HD) - classed as incidental
- No obvious dietary **palatability** issues for the AgAc treated groups; no effects on food consumption
- **Achieved doses** slightly lower than target doses (0, 0.4, 4, 40 mg/kg/d as AgAc) ▶ circa 75% of nominals:

Calculated[2] intake	F	0.3	3.1	27.8
(mg AgAc/kg bw/d)	M	0.3	2.8	25.4

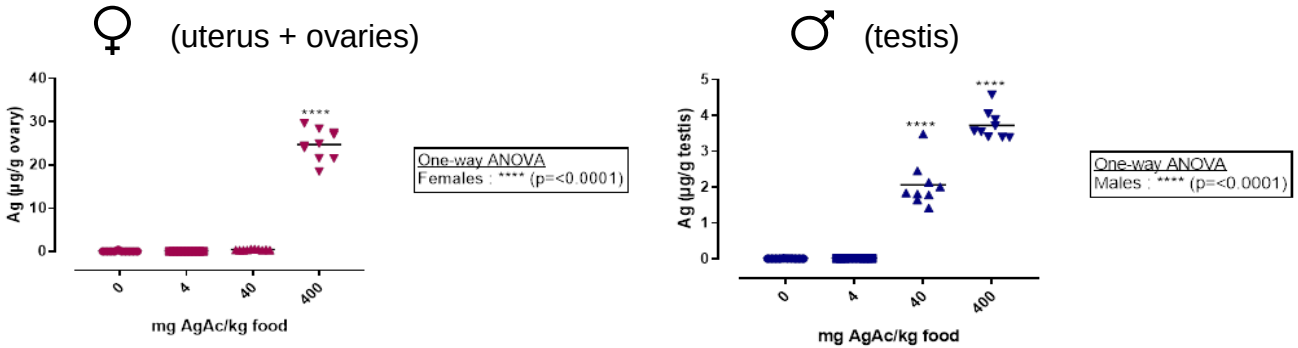
- **Bw gain** and **relative organ weights** (thymus, liver, kidney, spleen, repr. organs, brain): no significant effect of AgAc treatment

Enabling study gut microbiome: results (2/6)

- **Ag analysis in blood**: consistent with other studies; ♀ higher BA than ♂; oral BA higher via gavage than dietary admin; saturation kinetics not achieved (exposure levels too low)



- **Ag analysis in reproductive organs** (wk 10):
  - ♀: consistent with other studies
  - ♂: higher than other studies – to be further checked

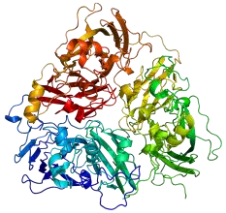


Enabling study gut microbiome: results (3/6)

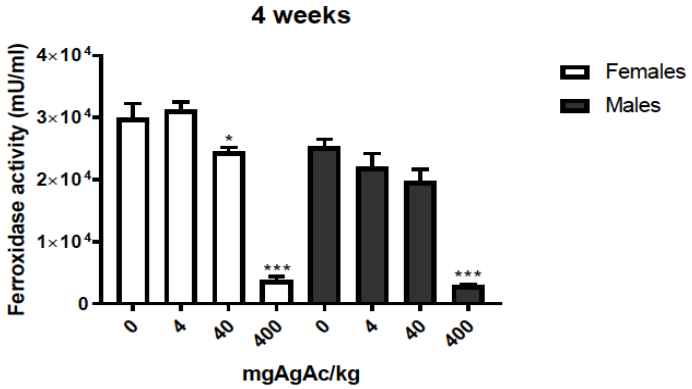
- **Biome** results:
  - Significant increase of **cyanobacteria** and significant reduction of **S24-7** in ♂ and ♀ after AgAc treatment
  - **α-diversity** (richness and evenness within a microbial community): no significant effect after AgAc treatment
  - **β-diversity** (differences in composition among communities; equilibrium of biome): dose-dependent effect in ♂ and ♀ after AgAc treatment (more pronounced in ♀)
  - Observed biome effects similar but not as pronounced as in other studies (nanoAg mouse study by vdBrule et al. 2016; AgAc rat study (gavage) by Williams et al. 2014)
  - Biological relevance of changes still being determined

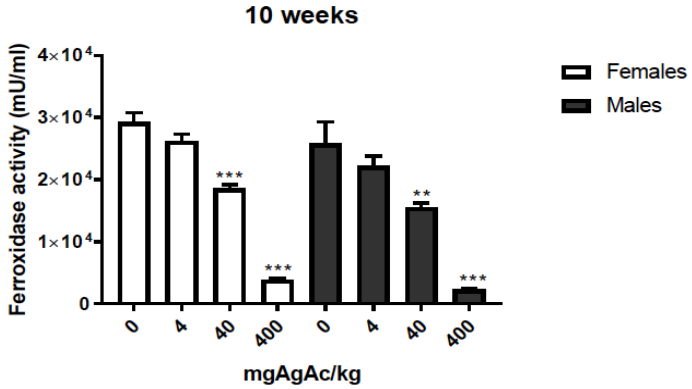
▶ **AgAc treatment has effect on the rat gut microbiome** (possibility of a potential secondary effect on reprotox?)

Enabling study gut microbiome: results (4/6)

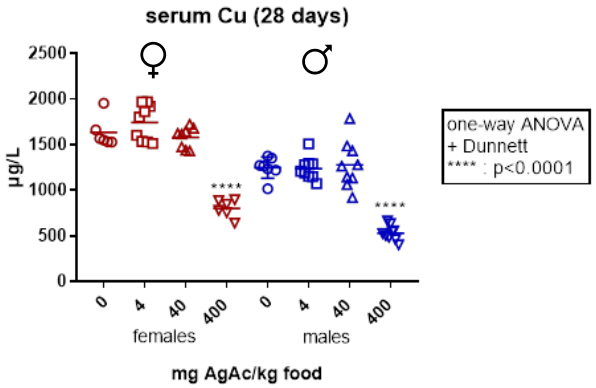


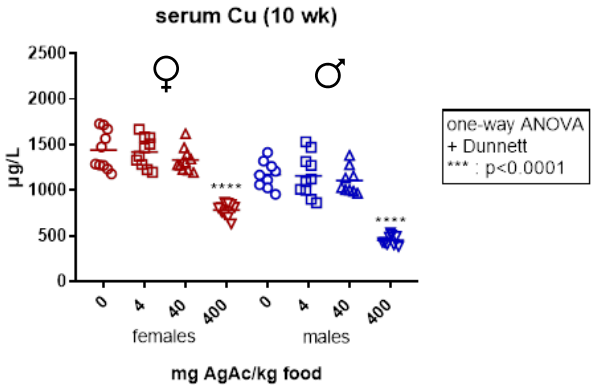
- **Serum ceruloplasmin (Cp) oxidase activity**:
  - clear dose-dependent reductions after AgAc treatment
  - effect very strong at HD (ED90) at which reprotox was observed by Sprando





- **Serum Cu levels**





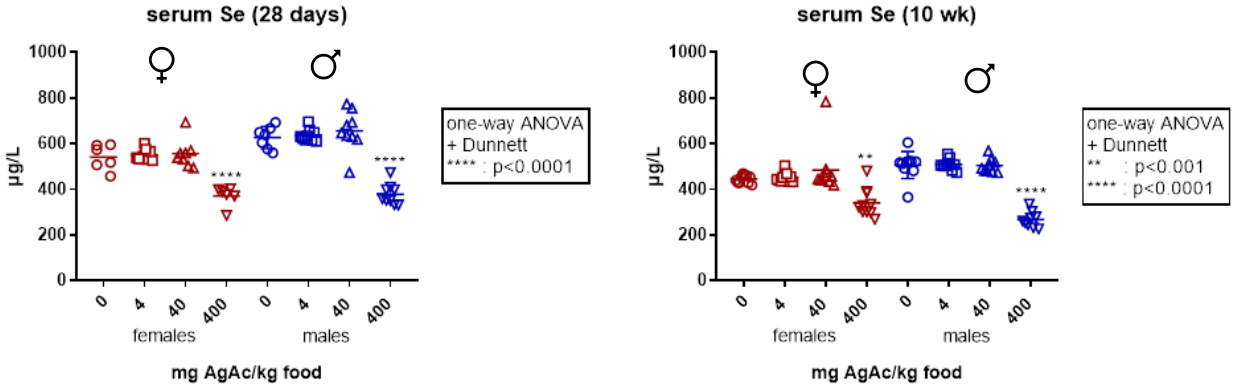
Enabling study gut microbiome: results (5/6)

	4-wk	10-wk
Serum Cu	49% of control	54% of control
Serum Cp oxidase activity	12% of control	12% of control

- **Serum Cu levels**
  - no depression of serum Cu levels up to ~ 3 mg AgAc/kg bw/d [♀] ▶ no expectation of any adverse dev tox
  - moderate induced Cu deficiency state at 28 mg AgAc/kg bw/d [♀] ▶ inferences regarding reprotox?
  - Sprando et al. OGRTS did not assess Cu markers, but dev tox was reported at 40 mg AgAc/kg bw/d; claimed dev tox LOAEL of 4 mg AgAc/kg bw/d
  - other relevant studies only provide fragmentary information… hint when degree of Cu depression becomes critical (<17%)
  - but complication: combined Cu / Cp effects caused by Ag

Enabling study gut microbiome: results (6/6)

- **Serum Se levels**



- previous report of Ag treatment effect on Se: Yoshida et al. 1983 ▶ similar Se reduction (but no reprotox parameters assessed)
- Se has a major role in healthy reproduction
- as independent effect, degree of Se depression unlikely to seriously affect ♀ / ♂ reproductive capacity; potential for adverse effect on pup growth?
- but: in the case of Ag, potential for combined effects factoring in also the Cu axis and reproductive impact potential
- **Se now confirmed as a parameter in respect of the EOGRTS design** (main study or enabling study)

Enabling study gut microbiome: conclusions so far

- **AgAc effects on rat biome**:
  - statistically significant
  - not as remarkable as expected based on previous study results but different mode of admin, different species, different silver form... + possibility of a very steep dose-response curve for biome effects
  - biological relevance of observed biome changes still needs to be determined

- Study has also moved forward our knowledge on **AgAc effects on Cp, Cu and Se**:
  - parameters to be taken into account for EOGRTS + further TK work
  - combined effect ▶ at what point does Ag^+ trigger Cu + Se + Cp deficiency?

- Number of **follow-up actions** still ongoing – see next slide

- Interpretation / comparison of available literature data complicated by different mode of admin (gavage / drinking water / diet) ▶ for Ag^+, there is no study comparing the effect of different mode of admins

Enabling study gut microbiome: follow-up work

- **Uterus and ovaries histopath** (control + HD)
- **Ultrastructural localisation** of Ag in the brain (does Ag pas BBB?) + Testis?
- **SCFA analysis**
  - Short-chain fatty acids (SCFAs) like butyric acid, lactic acid…
  - Key faeces metabolites generated by gut bacteria fermentation
  - Linked to functionality of biome
- **Estrogen analysis**
  - Circulating estrogen levels linked to functional microbiomes, such as the gut microbiome ▶ dysbiosis involving the GI tract has a potential to depress circulating estrogen
  - In the case of significant microbiome shifts, it is worth considering whether estrogen levels have been affected

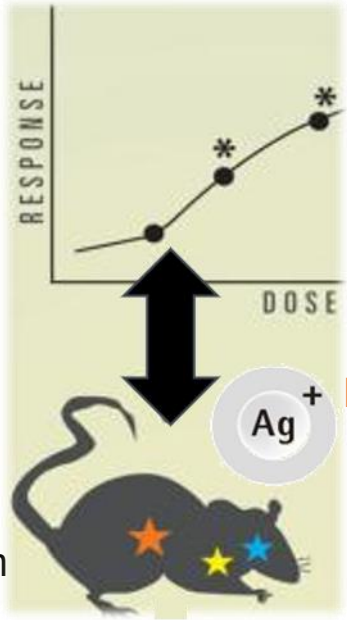
Science strategy: Ag read-across (1/3)
Background

Regulator-industry position

- ECHA and industry (EM) recognise complexities and need for improvement program (e.g. MISA)
- For Ag need is most immediate ▶ relatively data poor ▶ regulatory decisions imminent ▶ aggressive position of at least one MSCA
- Fix issue otherwise expect conservative regulation
- **Now a priority area to address**

But do what?

- EPMF and ESTF have outline vision for improved modelling / TK program
- Tiered strategy
- Discussed at joint EPMF/ESTF meeting Dec 2019



ESTF bioelution / read-across

- Used to fill SCAS data gaps (e.g. CM**R**)
- Validity increasingly challenged (KemI)
- For various technical reasons unlikely to always predict true bioavailability
- **ESTF now appreciate limitations of their existing approach**

EPMF bioelution / read-across

- Attempted bioelution model for various Ag forms (TK data was limited)
- Also unlikely to always reflect actual bioavailability *in vivo*
- **Little option when REACH dossiers prepared but standard bioelution approaches problematic for Ag**

Science strategy: Ag read-across (2/3)
Approach

Update read-across approach via adapted modelling plus verification testing (*in vivo*)

Tier 1	**Data-mine existing toxicokinetics (TK) data on major reference substances**: • Literature data mainly on nanoAg (massive Ag surrogate) but also $AgNO_3$, AgAc • TK data ESTF (from RDT studies)? • Take most reliable data and feed into bigger picture
Tier 2	**Improved *in vitro* bridging studies** • Ag: greater absorption expected post-gastric (i.e. in the intestine) because lower Cl content ► additional bioelution testing in intestinal fluids? • Similar testing performed for other metals (e.g. Ni compounds) • Preliminary cost estimate for combined 'gastric / post-gastric' bioelution <70 k€ total
Tier 3	Validation of *in vitro* models by ***in vivo* TK testing** on a limited number of Ag substances, selected based on the results of the *in vitro* testing Approx. 30 k€ per test item (current best guess 5 test articles)

Science strategy: Ag read-across (3/3)
Tier 1: Ag TK data mining

Messy & fragmentary dataset!

But several take-homes evident

Tier 3 (+PBTK)

~~*Tier 2*~~

Ionic Ag ref. substance ▶ Bioavailability of AgAc (rat models) at least as high as $AgNO_3$

AgNP ▶ Bioavailability is less than ionic Ag but still can be appreciable

For AgNP TK there are complicating factors ▶ including influence of ionic Ag formed in situ

TK of bulk Ag^0 (≥ micron size) not yet established (but likely ≠ from AgNP) ▶ major implications if AgNP used as read-across ▶ priority should be differentiating TK efforts

Bioelution models for Ag ▶ problematic ▶ easier to do comparative conventional TK studies

PBTK models ▶ more potential ▶ independent validity assessment & further calibration with more in vivo data necessary for this option

Science strategy: TK work (Tier 3)
Aims

- Need further supporting test data for read-across approach
- Available **Ag TK** is a patch-work of studies & overall confidence level not optimal ▶ emphasis on proper comparative *in vivo* TK (at least key Ag substances) + potentially modelling (PBTK)
- Ideally differentiate between:
  - elemental Ag and ionic Ag
  - elemental Ag from AgNP
- Suggested test substances for *in vivo* testing:
  - AgAc
  - $AgNO_3$
  - elemental Ag^0 (micron-sized form without nano)
  - elemental AgNP
  - (AgCl, Ag_2O)
- Possible add-ons:
  - Dose range finder aspects
  - Mode of admin aspects
  - Mechanistic angles

Science strategy: preparation EOGRTS (1/4)
Dose level setting

1. Consider all **TK** information (adults, embryofetal, lactational transfer etc.)

   If TK saturation evident (e.g. absorption in P animals) ► basis for setting HD especially if above human exposure

2. Set HD based on evidence of **"some toxicity"** (or else set as limit dose)

   For example: 10% ↓ in bwt vs controls.
   Toxicity in ♂ and ♀ should be considered.

3. Other factors:
   Secondary toxicity (e.g. biome effects), mechanistic, human exposure level (not primary consideration), regulatory thresholds (CLP etc.)

4. **Final dose level proposal along with justification**

Based on OECD TG443 guidance

R.7a guidance emphasis differs: demonstration of some tox at HD is more important criterion than TK

How: Assessment of systemic toxicity and reproductive toxicity reference doses for AgAc

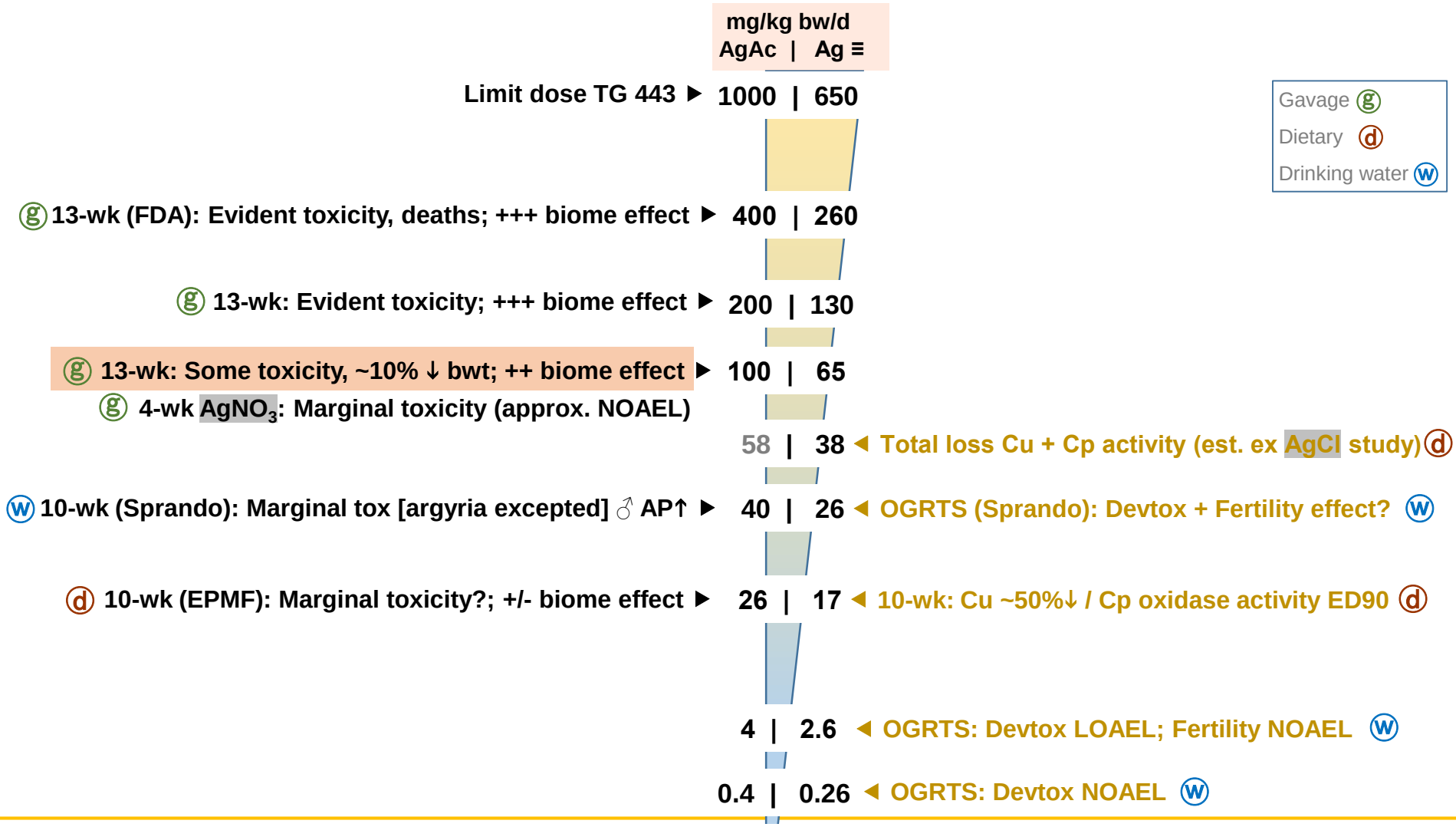
See next slide

Legitimate to consider other factors in dose-setting - demonstration of secondary toxicity potential

Options to do more enabling work, e.g. TK, DRF studies, other supporting studies

Imperative to get dose-setting right: EOGRTS is a one-shot opportunity!

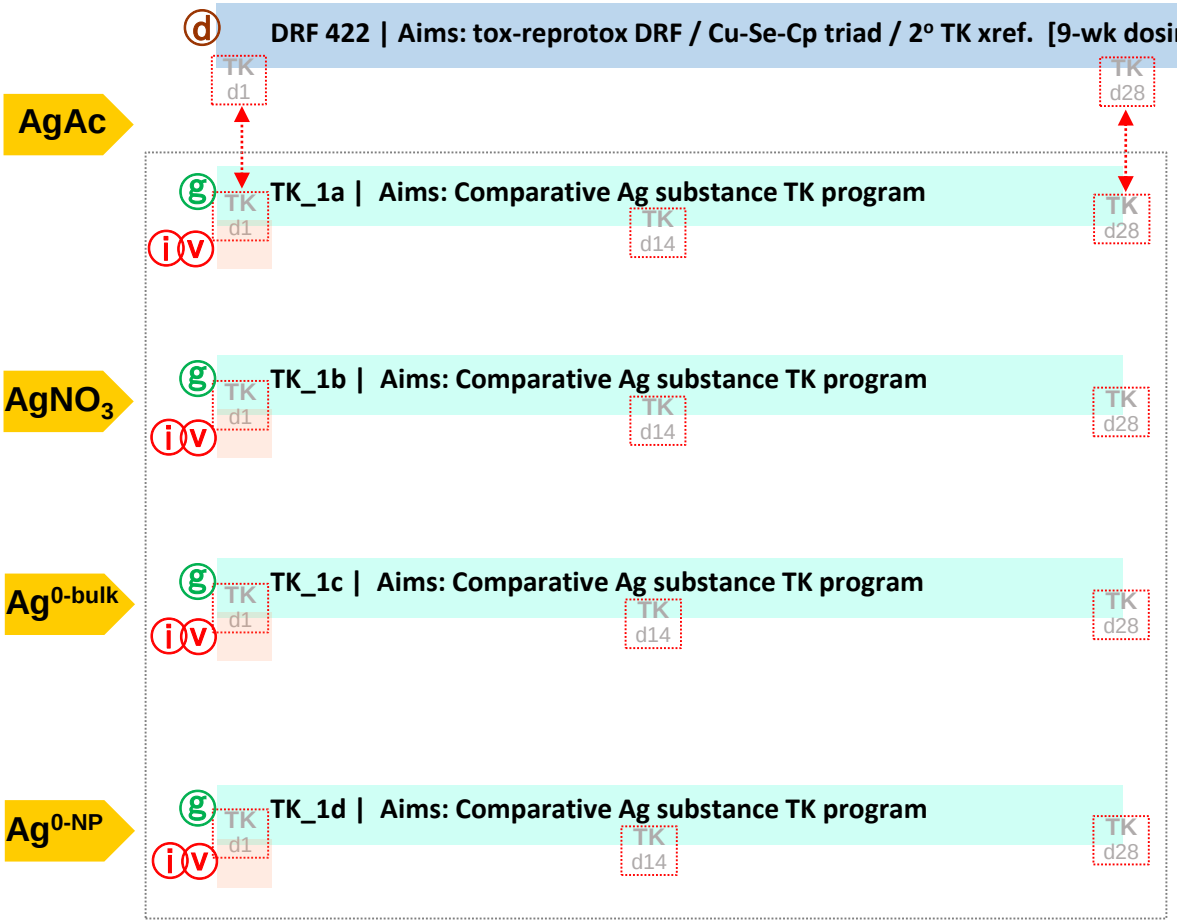
Science strategy: preparation EOGRTS (2/4)
Dose level vs effect info



Science strategy: preparation EOGRTS (3/4)
Dose setting

- Current available effect data considered insufficient for definitive dose setting for the EOGRTS ▶ **further DRF work needed**
- Dietary admin for EOGRTS ▶ enabling DRF work to be configured accordingly (disadvantage: you cannot get same precision than with gavage)
- Suggested HD for DRF: 125 mg AgAc/kg bw/d (given 'some tox' observed at 100 mg AgAc/kg bw/d via gavage and we would have to go slightly higher for dietary admin); total of 4 doses suggested to ensure proper identification NOAEL/LOAEL
- Proposed study design (see next slide):
  - **DRF**: **dietary OECD 422** study with AgAc, measuring usual parameters + Cu, Se, Cp parameters (given biome study has confirmed importance of Ag^+ effect on Cu, Se, Cp) + **TK** parameters
  - **TK**: dietary mode has some disadvantages (e.g. impossible to derive absolute BA, higher inter-individual TK variability) ▶ concurrent **TK** studies (~OECD 417) for elemental Ag (micro), elemental nanoAg and $AgNO_3$ according to more conventional TK design **gavage-i.v. couplet** ▶ possibility to derive absolute BA + some other technical advantages when considering our aim of establishing definitive comparative TK between Ag substances for read-across, and maybe also a dataset that could be used to calibrate a PBTK model

Science strategy: preparation EOGRTS (4/4)
Suggested study design DRF + TK



- Systemic toxicity – dose setting
- Basal reprotox indices
- In life Cu/Se/Cp. Se-enzyme(s)
- Terminal tissue Cu/Se (tissue Cp?)
- Placental & embryofetal TK [Ag]
- Admin. mode cross-reference TK
- Reserve biome samples @ termination?

- Gavage repeated dosing (steady state blood values)
- d1 single i.v. dose separate satellite groups
- Absolute bioavailability
- Absorption biokinetics d1>d28 [0-72 h measurements]
- Critical tissue distribution [Ag] – gut, CNS, reproductive, bone marrow, liver/spleen, others?
- Key comparator & read-across TK dataset

- Parameters as TK segment above
- Run as concurrent study

- Parameters as TK segment above
- Run as concurrent study
- Low micron-size Ag should be feasible by i.v.

- Parameters as TK segment above
- Run as concurrent study

To be further discussed by Tox Experts

Gavage (g)
Dietary (d)
Intravenous (iv)

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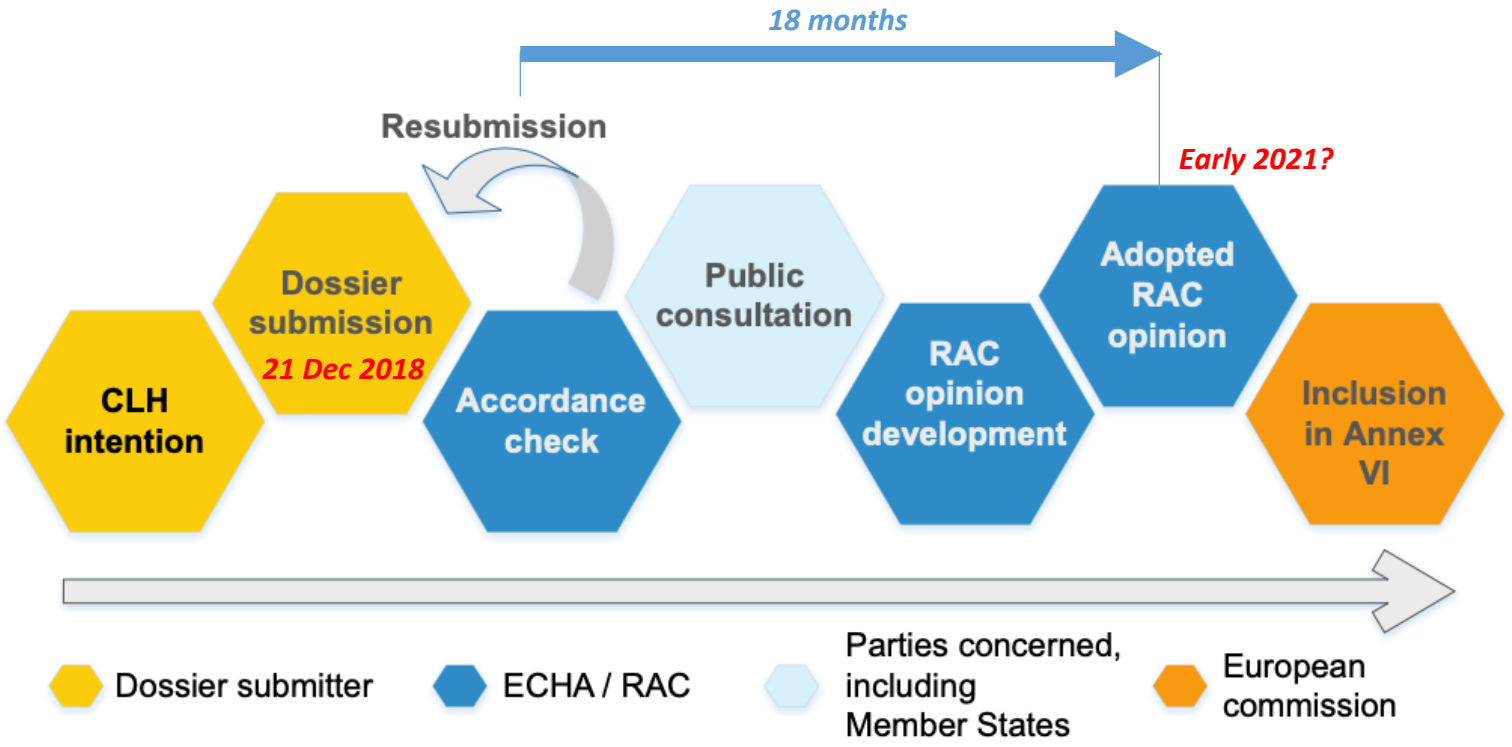
CLH proposal silver nitrate

CLH proposal silver nitrate – process and timing



→ RAC opinion CLH before EOGRTS test results available?

(EOGRTS test results likely available before inclusion in ATP (2022))

Silver nitrate CLH – HH endpoint proposals vs. WoE (1/3)

- **Acute Tox 2**
  - Based on poor-quality dataset
  - Refer to $AgNO_3$ study performed by ESTF (no mortality observed at HD)
- **Skin Corr 1A**
  - Based on EPMF performed OECD 431 study (2009), which - at the time it was performed - was not validated for subcategorization
  - Several datasets of additional *in vitro* test data since (not assessed by Kemi), belonging to inter-lab validation series for latest version of TG 431 (adopted by OECD Jul 2016):
    - EST-1000: 1A
    - EpiSkin: 2/3 1B; 1/3 1A → 1B
    - EpiDerm: 1A
    - SkinEthic RHE: 1A
    - EpiCS: 1A
  - WoE: **Skin Corr 1A** but EpiSkin demonstrated to have a higher accuracy in respect of correct subcategorization (less prone to over-categorising 1BC as 1A, whereas it still has acceptable performance in not under-classifying true 1A)

FOR DISCUSSION

Silver nitrate CLH – HH endpoint proposals vs. WoE (2/3)

- **Skin Sens 1**
  - Human evidence very low
  - Kemi refers to 2 animal studies with other Ag substances, response seems insufficient for classification

- **Muta 2**
  - Kemi only selected part of the available Ag dataset to serve their own agenda, while there are more studies available to support a non-classification
  - Overview table of all available data in preparation clearly showing that the evidence to support a classification is not convincing
  - Review by Kirkland?

Silver nitrate CLH – HH endpoint proposals vs. WoE (3/3)

- **Repr 1B**
  - **Fertility**:
    - Kemi used Sprando study fertility outcomes, 2-gen studies on SCAS, and inconsistent evidence from low-grade studies on nanosilver as a basis for classification
    - Points of leverage regarding these datasets in respect of the fertility endpoint
    - Recycle some of our comments used for the SZZ CLH public consultation + comments Sprando study. For nanoAg studies: use a tabular approach listing the KL scores + refer to fact that histopath evidence for testicular effects is not available
  - **Development:**
    - Sprando study and the 2-gen study with SZZ are most adverse
    - Recycle some of our comments used for the SZZ CLH + point out weaknesses in the Sprando study and stress need for an EOGRTS to fill the datagap

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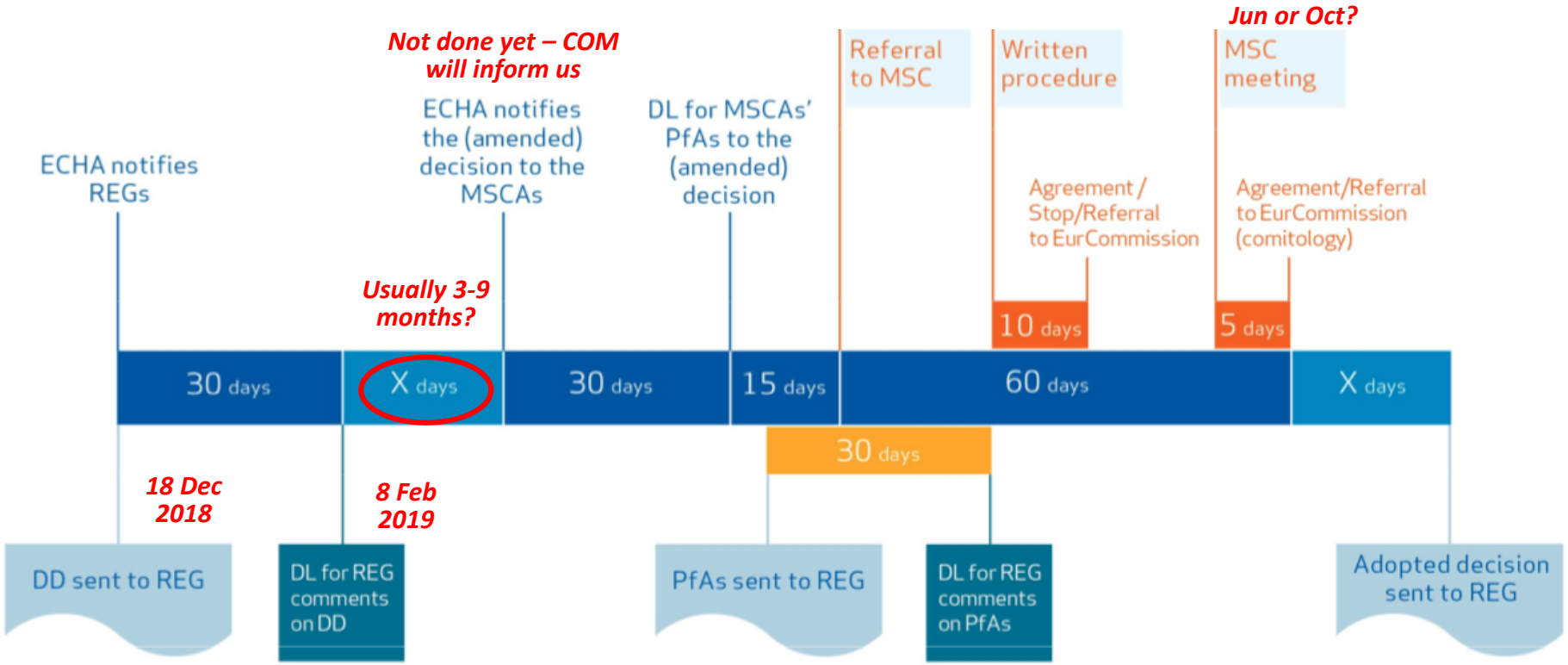
Advocacy strategy silver reprotox

Advocacy strategy – Defence TP



NB: A decision can be adopted directly if no PfAs are received.

Opportunities to defend TP:

- PfAs MSCAs (and written comments) ► contact key MSCAs *(slide follows)*
- MSC meeting (if no written procedure)

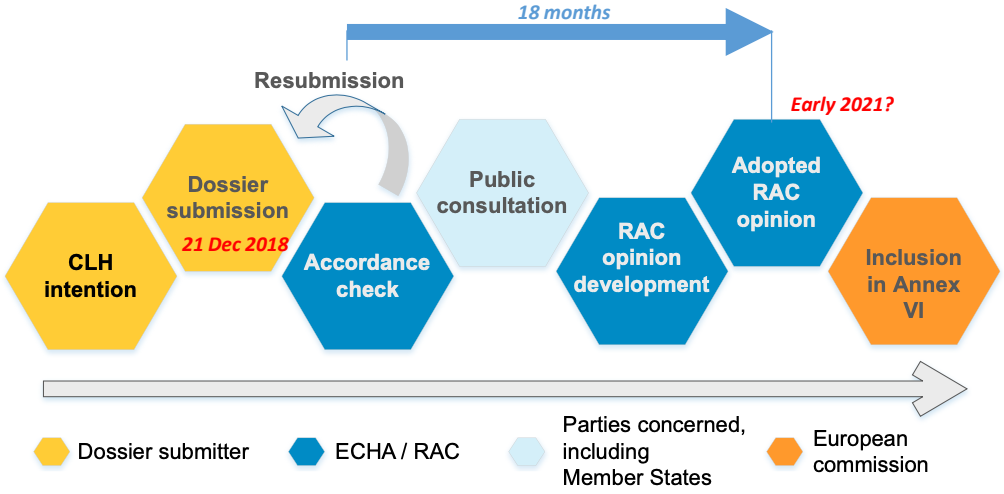
Advocacy strategy – BPR vs REACH

REACH ▶ EOGRTS TP:

- Draft decision Dec 2018 in agreement with proposal
- Final decision expected between Jun 2019 and Feb 2020
- EOGRTS test results not available before **mid-2021 at the earliest**

BPR ▶ CLH $AgNO_3$ by Kemi incl. Repr Cat. 1B:

- Dossier still in accordance check phase
- Once complete, ECHA will launch PC and CLH process will start



- ▶ RAC opinion CLH $AgNO_3$ before EOGRTS test results available?
- ▶ EOGRTS TP rejected due to ongoing CLH?

- Similar proposals Ag and AgCl expected spring 2019

Advocacy strategy – Meetings authorities disconnect REACH/BPR (1/3)

Meeting ECHA 8 Feb 2019

- Stella Jones (ECHA acting HoU Classification) and Jos Mossink (ECHA HoU SID and on behalf of MISA)
- EPMF request joint meeting (all involved actors Ag REACH / BPR / CLH) ▶ ECHA cannot bring all actors together
- ECHA confirmed that they had contacted Kemi and informed them about the ongoing TPE; Kemi acknowledged
- Once CLH dossier compliant, ECHA will be obliged to launch CLH process by a PC and ending at ECHA with the RAC opinion (18 months); then CLH goes to Commission
- If EOGRTS outcome available on time before inclusion into ATP, Commission can send the dossier back to RAC (art. 77(3))
- ECHA recommended **bilateral meetings with Kemi and European Commission** and asked to be kept informed

Advocacy strategy – Meetings authorities disconnect REACH/BPR (2/3)

Meeting **European Commission** 13 March 2019

- DG ENV (Katrin Schutte, Sylvain Bintein, Andrej Kobe), DG GROW (Peter Baricic), DG SANTE (Ludovic Chatelin)
- EPMF concerns on ongoing processes REACH/BPR and overlap between CLH proposal Kemi and TPE under REACH
- Data gaps regarding Ag^+ reprotox ▶ current data insufficient to classify AgNO3 / Ag^+ as Repro 1B! Further significant data expected from EOGRTS
- DG SANTE confirmed that Kemi waits for RAC opinion to be able to go to BPC – DG SANTE cannot delay CLH process (dossier pending since 2007!)
- Suggestion to **raise our arguments during PC** so RAC can take them into account during the scientific discussion
- DG ENV could also inform RAC about ongoing EOGRTS TP and ask RAC to take this in their opinion. **RAC cannot delay its opinion (18 months period starts with PC) but could include in their conclusions an opinion whether the classification may be changed or not by the EOGRTS outcome**. This could be triggered by a specific question from COM but feasibility of this needs to be checked with ECHA and RAC.
- DG ENV needs clear view on added value EOGRTS ▶ **EPMF table sent 29 March**

Advocacy strategy – Meetings authorities disconnect REACH/BPR (3/3)

Call Kemi 21 March 2019

- Ulrike Frank, Katarina Lundberg (BPR)
- EPMF defended need for additional data before concluding on classification and stressed ECHA support for TP
- Further clarification timing CLH:
  - Resubmission $AgNO_3$ CLH in April
  - Next SCAS: elemental Ag ▶ submission CLH sometime during spring
- **Kemi agreed current data is insufficient** and confirmed that 2 timelines (CLH and TP) will probably not match
- **Postponing CLH not an option** given time pressure by Commission
  - Deadline 2024 to conclude BPR assessments
  - CLH pre-condition to submit CAR under BPR
  - $AgNO_3$ dossier from ESTF very data poor ▶ data requirements on C and M endpoints currently not fulfilled BUT Kemi cannot make C/M testing requirements if they believe substance already falls under exclusion criteria because of Repr 1B classification
  - If RAC agrees on Repr 1B ▶ substance fulfils exclusion criteria under BPR and further C/M testing becomes unnecessary
  - If RAC does not agree on Repr 1B ▶ BPR process continues and Kemi needs to request C/M testing

Advocacy strategy – Actions (1/2)

Actions conducted:

- Development MFA for Ag ► demonstrate importance of Ag uses and exposure control;
- Summary sheet on socio-economic importance of silver

Actions foreseen:

- Stakeholders mapping including a DUs mapping (cf. background doc);

EU Institution	Available industry network (including DUs)	Contact persons	Date of meeting/exchanges	Outcome				Follow-up
				Receptivity	Potential to influence CLH process	Potential to influence EOGRTs process	Comments	
DG Grow	Violaine Verougstraete (EM) (verougstraete@eurometaux.be) France Capon (EPMF) (france.capon@epmf.be)	Peter Baricic (Peter.BARICIC@ec.europa.eu) An Jamers (An.JAMERS@ec.europa.eu)	13/03/2019	Medium	Medium	No influence		
DG Environment	Michael Di Rienzo (Silver Institute) (MDiRienzo@silverinstitute.org) Ruth Crowell (LBMA) (Ruth.Crowell@lbma.org.uk) Ian Watt/Andrew Goodyear (ESTF) (IWatt@dow.com ; andrew.goodyear@erm.com)	Sylvain Bintein (Sylvain.BINTEIN@ec.europa.eu) Katrin Schutte (Katrin.SCHUTTE@ec.europa.eu) Andrej Kobe (Andrej.KOBE@ec.europa.eu)	13/03/2019	High	High	High	They requested more scientific information on the added value of EOGRTs to fill in existing gaps for	The table was sent to EC on 27/03 in preparation of a conf call between EC and ECHA Classification unit on

Country	Available industry network (including DUs)	MSCAs EPG member Environmental Attaché in Brussels REACH Committee member	Date of meeting/exchange	Outcome				Follow-up
				Receptivity	Potential for MSCAs to intervene in the CLH process	Potential for MSCAs to intervene in the TPs process	Comments	
Austria	Juliana Karall (WKO) (julianna.karall@wko.at) No EPMF members No major DUs identified	Mr Thomas Jakl Mr Martin Wimmer Mr Georg Knoflach Ms Cosima Hufler Ms Eva Mittermayr Martin Wimmer (REACH Committee)						
Belgium	Patrick van den Bossche (Agoria) (patrick.vandenbossche@agoria.be)	Ms Aurélie Dussart Ms Catherine Dantine						

Key MS: High priority: **Belgium, Germany, Italy, Poland, Sweden**

Medium priority: Bulgaria, Finland, France, The Netherlands, UK

- DU communication plan including key messages on the process

Advocacy strategy – Actions (2/2)

Actions foreseen (continued):

- Creation **Ag advocacy group** to be able to react quickly to the latest developments and ensure that the secretariat receives the adequate input of the members in a short period of time
- Prepare for CLH public consultation and CLH discussion at RAC
- Inform a series of key MS of the situation to find allies in the two processes (cf. stakeholders mapping)
- Start high political advocacy to stop the CLH proposal creating alliances with key DUs (a DUs mapping is ongoing)

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Inclusion of silver acetate in the EPMF portfolio

Inclusion of silver acetate in the EPMF portfolio

- AgAc currently not in EPMF portfolio but recent interest for registration (1-10 t/a) + test substance for EOGRTS
- Data gap analysis: testing required for:
  - Flammability
  - Auto-flammability
  - Granulometry
  - Skin irritation *in vitro*
  - Eye irritation *in vitro*
  - 24h TDp screening test (for read-across purposes)
  - pH (for possible waiving skin sensitisation / acute oral study)
- ± 25 k€

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Workplan and Budget 2020

2020 Budget – REACH platforms

1. Ag metal (including nano)	266.536 €			0,8
1.1 REACH registration	0 €			
1.2 REACH dossier maintenance	93.500 €			
1.3 REACH evaluation	0 €			
1.4 REACH classification & labelling	20.000 €			
1.5 REACH authorisation	0 €			
1.6 Internal and external fixed Scientific Managers	142.236 €			
1.7 IUCLID IT hosting system	400 €			
1.8 Knowledge Management tool + hosting	400 €			
1.9 Science budget	10.000 €			
2. Ag compounds	297.536 €			0,8
2.1 REACH registration	0 €			
2.2 REACH dossier maintenance	124.500 €			
2.3 REACH evaluation	0 €			
2.4 REACH classification & labelling	20.000 €			
2.5 REACH authorisation	0 €			
2.6 Internal and external fixed Scientific Managers	142.236 €			
2.7 IUCLID IT hosting system	400 €			
2.8 Knowledge Management tool + hosting	400 €			
2.9 Science budget	10.000 €			

2020 Budget – non-REACH platform

2. Silver EQS	**90.758 €**			**0,2**
2.1 Science budget	**10.000 €**			
2.2 Internal and external fixed Scientific Managers	**50.758 €**			
2.3 Advocacy	**30.000 €**			

AOB, next meetings/calls and closing remarks

LR change due to Brexit

- As a result of Brexit discussions, need to change Lead Registrant positions from JM

Name of the substance	Identification numbers		Tonnage band	Proposed NEW LR
	CAS	EC		
Silver carbonate	534-16-7	208-590-3	1-10 t/a	**Saxonia**
Disilver(1+) sulphate	10294-26-5	233-653-7	1-10 t/a	**Metalor**

FOR APPROVAL

Next Ag WG meetings:

- **8 October 2019**

THANK YOU

www.epmf.be | info@epmf.be

Avenue de Broqueville 12, B-1150 Brussels
+32 (0)2 761 01 00