Precious Metals Consortium

Precious Metals & Rhenium Consortium

Silver Work Group Meeting

15 March 2018 | Brussels

Precious Metals Consortium

1. Welcome and introduction

Rob Garrett (Ames, United Kingdom)

1.1 Reminder on confidentiality and competition law

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 Agreement complies with the provisions of the REACH Regulation.
Consultation in Matters of Competition Law	
Consult an in-house legal expert or the compliance officer of your company or an external lawyer whenever there are uncertainties respecting compliance with competition law. Stop all meetings/discussions which are not in compliance with these Compliance Guidelines until a legal expert has been involved.	Don't assume that these Compliance Guidelines deal with all competition law issues exhaustively. Basically, compliance with Art. 101 and 102 TFEU can be determined only on the basis of market impact in each individual case. These Compliance Guidelines may therefore be regarded only as a means of providing general conduct recommendations.
Activities in any preliminary phase and at any other stage of operation of the Consortium	
Restrict cooperation within the scope of the preliminary phase to the initially defined goals and purposes of the cooperation.	Pursuant to Art. 101 and 102 TFEU, activities which have the object of the effect of preventing, restricting and/or distorting competition are prohibited within the scope of this Agreement, including: - Coming to agreement, including arrangements or collusions, about prices, markets and customers (see Art. 101 paragraph 1 a)-e) TFEU); - Joint boycotting of other companies; - The unjustified unequal treatment of trade partners; - The abusive exploitation of a dominating market position.
Exchange of Confidential Information	
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 parties of the Agreement. Stop all meetings which are not in compliance with these Guidelines until a legal expert has been involved.	

1.2 Tour de table and apologies

- Cf. participants list included in agenda

1.3 Approval of the agenda

1. Welcome and Introduction
   - 1.1 Reminder on Confidentiality and Competition Law
   - 1.2. Tour de table and apologies
   - 1.3. Approval of the agenda
   - 1.4. Approval of the minutes of the last meetings/calls and status of action points
   - 1.5. Election new chair / co-chair
2. Water Framework Directive (WFD) silver prioritisation
   - 2.1 Process and timeline
   - 2.2. Revision silver PNEC / EQS: update on discussions WG Chemicals Ag sub-group
   - 2.3. Additional ecotox testing

Coffee break

3. Silver reproductive toxicity
   - 3.1 Recap current situation silver reprotox
   - 3.2. Status EOGRTS Testing Proposal
   - 3.3. PMC strategy
   - 3.4. Outcome Tox Expert discussions
   - 3.5. Enabling study gut microbiome
   - 3.6. Status CLH proposals silver active substances (SCAS)
4. Workplan and budget
5. AOB, next meetings/calls and closing remarks

FOR APPROVAL

1.4 Approval of the minutes of the last meetings/calls and status of action points: WG meeting 19 Oct

	What?	Who?	Status
Water Framework Directive (WFD) prioritisation			
1	Circulate assessment Ag chronic freshwater dataset + updated PNEC derivation	PMC Sec	**DONE**
2	Organise call Ag WG to discuss updated PNEC derivation	PMC Sec	**DONE**
3	Check Ag ERVs for classification purposes + consider costs/timelines of further work on Ag bioavailability	PMC Sec	**ONGOING**
4	If the REACH $PNEC_{sed}$ is questioned by the Ag sub-group, challenge ESTF study (suggest REACH $PNEC_{sed}$ as provisional) and address data gap with well-designed sediment tests	PMC Sec	**NOT DONE (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	**NOT DONE (During PC)**
6	Contact Kemi for a meeting early 2018 to discuss the review of elemental silver	PMC Sec	**NOT DONE (Wait for DD)**
Testing proposal EOGRTS			
7	Check EFSA position on Babu et al. 2016 study	N Rajapakse	**DONE**
8	Perform Ag HH literature reviews more regularly to ensure we do not miss important publications	PMC Sec	**ONGOING**
9	Expert technical discussion on the feasibility of enabling work and how to revise our TP	Tox Experts	**ONGOING**
10	Recommendation to the PMC Mgmt Cttee on enabling work for our TP (start now or wait)	Ag WG	
11	Decision on enabling work for our TP	PMC Mgmt Cttee	
12	Check possibility to withdraw our TP with Eurométaux / informally with ECHA	PMC Sec	**DONE**
13	Try to convince ESTF of the defence imperatives arising from the possibility that Repr Cat. 2 classification becomes Cat. 1B	PMC Sec	**NOT DONE (For discussion)**
2018 budget			
14	Add 150 k€ for the additional sediment tests and budget 1.5 million € for the EOGRTS	PMC Sec	**DONE**

APPROVAL OF DRAFT MINUTES 19 Oct?

1.4 Approval of the minutes of the last meetings/calls and status of action points: Call 9 Nov reprotox

	What?	Who?	Status
1	Check who contact person at ECHA will be for our TP	PMC Sec	DONE
2	Review DU mapping and finalise SEA data gathering for silver, in order to identify key DUs to be contacted	PMC Sec	ONGOING
3	Contact key DUs in order to develop arguments towards authorities on classification impact, to have available if needed	PMC Sec	ONGOING
4	Consider key themes for Holsapple meeting (cf. slides 6-7 in Annex) and suggest additional themes to PMC Sec if any	Ag WG	DONE
5	Send Holsapple 1 or more CLH proposals SCAS + example RAC decisions Repr classification borates	PMC Sec	DONE
6	Provide PMC Sec with other possible test cases on RAC decisions Repr classification if any	Ag WG	DONE
7	Check with Eurométaux if there are test cases on MSC decisions Repr TP (incl. comments different MS)	PMC Sec with EM	DONE
8	Follow up updated literature survey on Ag mamm tox (i.e.: Klimisch analysis; evaluation of importance / contribution to Ag dataset; level of congruence with existing information; evaluation of whether they are likely to feature in regulatory decision making)	PMC Sec with M. Raffray	DONE
9	Consider 'stress-testing examples' for Holsapple meeting (cf. slides 8-9 in Annex) and suggest additional ones to PMC Sec if any	Ag WG	DONE
10	Draft agenda for 23 Nov mtg	PMC Sec with M Raffray	DONE
11	Re-check argumentation that disruption of Cu homeostasis caused by Ag is an indirect effect	PMC Sec with EM	NOT DONE (For discussion)
12	Check paper from Williams et al. 2014 (http://www.tandfonline.com/doi/full/10.3109/17435390.2014.921346)	Ag WG	DONE

APPROVAL OF DRAFT MINUTES 9 Nov?

1.4 Approval of the minutes of the last meetings/calls and status of action points: TE meeting 23 Nov reprotox

	What?	Who?	Status
1	Write an expert paragraph on the adversity / dose-response of the Babu et al. study's immunophenotyping effect with depression in cell populations	M Holsapple	DONE
2	Send WHO reference that mentions NOAEL of 5 µg/kg bw/day	M Holsapple	DONE
3	Check with IMOA (S. Carey) argumentation of the dose-setting for Mo	PMC Sec	ONGOING
4	Contact expert on the gut microbiome (D. Lison?) for experimental design of enabling studies / get opinion on the Van den Brule et al. paper and whether or not results can be extrapolated to the rat	PMC Sec	DONE
5	Approach ESTF again on possible Repr classification	PMC Sec	NOT DONE (For discussion)
6	Include human relevance gut microbiome MoA in stress-test	S.Verberckmoes	ONGOING
7	Check what parameter to use to measure adverse effect	O Lemke	ONGOING
8	Check with IZA (N. Lombaert) how they have argumented the Zn case	PMC Sec	ONGOING
9	Look at EOGRTS guidance (OECD TG 443) and see what adjustment is needed to extend DIT protocol to include juvenile animals and young adults	M Holsapple	DONE
10	Reflect on DNT expert and send suggestions to PMC Secretariat	M Holsapple	DONE
11	Contact D. Lison re the van den Brule et al. paper / expert consultancy possibilities	S Verberckmoes	DONE

APPROVAL OF DRAFT MINUTES 23 Nov?

1.5 Election new chair / co-chair

- PMC & EPMF restructuration:
  - Change into platforms (Ag / Ag compounds) but similar approach for WG (Ag WG)
  - Proposal to have chair + co-chair for each WG, mandate of 3 years
  - Decision Mgmt Cttee meeting Feb: install immediately after approval
- **Chair** candidate: Clémence Siret (SAFT)
- **Co-chair** candidate: Rob Garrett (Ames Goldsmith)
- Effective after approval until 2021

FOR APPROVAL

Precious Metals Consortium

2. Water Framework Directive (WFD) silver prioritisation

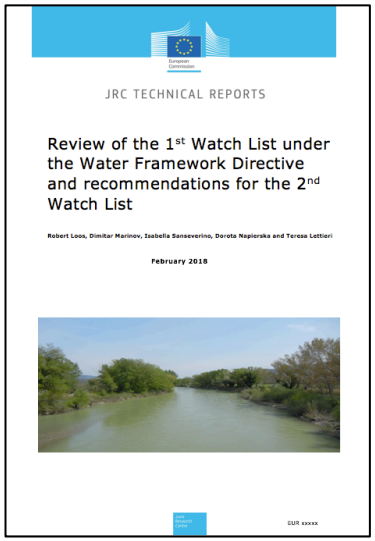
2.1 Process and timeline: reminder

- **Monitoring based exercise** JRC: Ag mentioned in short list of potential PS / substances under further consideration for EQS derivation (STE score > 1.8)

- First draft **EQS dossier** by JRC: freshwater EQS of 10 ng/L proposed versus REACH PNEC of 40 ng/L

- March 2017 EC proposed **process & timeline** for review of PS list / WL:
  - **PS list**: confirmation of **PNEC** → re-run STE-score & conclude on shortlisting
  - PNECs to be discussed in **substance-specific sub-groups** → MS invited to lead
  - Silver: MS invited to send more **monitoring data**
  - Output of review PS list and use of work: **EQSs harmonised at EU-level** → MS encouraged to take into account shortlisted substances for 3rd RBMP
  - Output of review PS list may include identification of substances for which analysis shows potential risk at EU level, but for which insufficient monitoring data to conclude → considered for inclusion in **WL**

2.1 Process and timeline: status (1)

- 

  WL report JRC:

  silver not proposed for WL

- **Further monitoring data Ag**
  - Combined with data previously used in the prioritisation: fulfil min. requirements for nr of MS / sites / samples used under the previous prioritisation
  - JRC calculated **new STE score < 1.8** (using PNEC of 10 ng/L)
  - STE score > 1.8 was criterion for shortlisting
    - ➢ Oct WG Chem meeting: COM replied that it is important to **wait until outcome of work on Ag EQS** to conclude whether Ag poses a significant risk at EU level

2.1 Process and timeline: status (2)

- **Silver specific sub-group**
  - **Sweden** (lead), Germany, Latvia, Denmark, France, EM & PMC
  - Original aim: agree on EQS early 2018 for all matrices that could be of relevance, incl. sediment → dossier to be presented to SCHEER
  - Starting point: JRC report, available studies from REACH, RIVM Ag ERL report, BPR, literature
  - Discussions still ongoing (cf. next slides)
- **European Commission**
  - WG Chem Meetings Oct 2017 & Jan 2018: PS list not a priority… focus on WL
  - Next WG Chem meeting 17-18 Apr 2018
  - Still unclear how work substance-specific sub-groups will be aligned with COM call for tenders "Water pollutant quality standards and monitoring”
  - Timing for PS still unclear

2.2 Revision silver PNEC / EQS: update on discussions WG Chemicals Ag Sub-Group

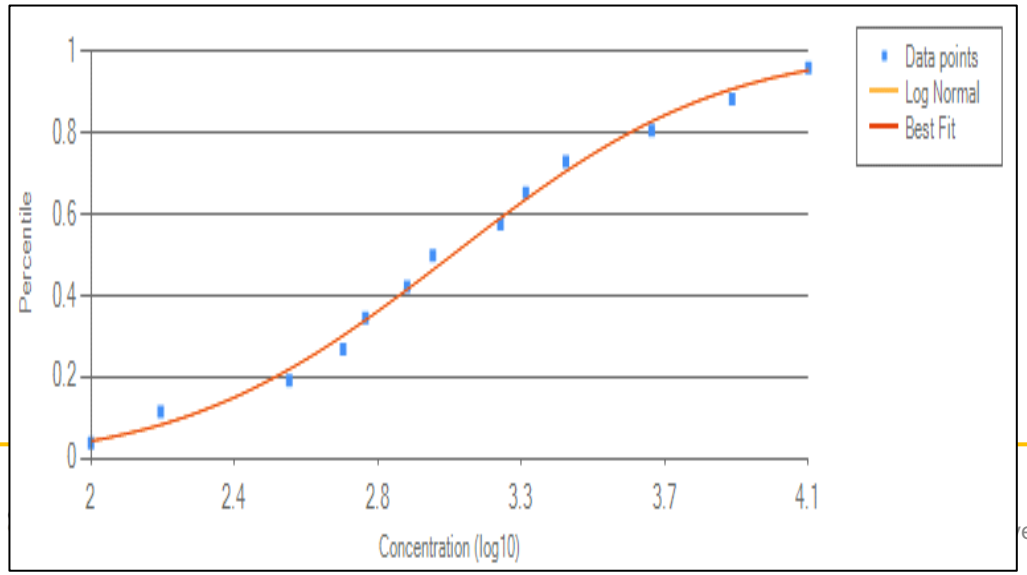
PMC revision silver PNEC/EQS freshwater (1)

- (Re-)assessed data: new studies + previous studies REACH CSR / RIVM (+ comparison with PNEC derivations from REACH CSR / RIVM)
- **Data selection criteria** in line with:
  - EQS guidance
  - MERAG criteria
  - RIVM criteria, except for low **DOC**
    - Ag sub-group agreed that there is currently not enough data available to conclude that DOC influences chronic Ag toxicity
- Some data previously considered for PNEC not valid (nominal values)
- Report circulated to WG Dec 2017

PMC revision silver PNEC/EQS freshwater (2)

Species	Endpoint	NOEC/EC10 (µg/L)
Ceriodaphnia dubia	reproduction	4.360
Chironomus tentans	growth	12.540
Chlamydomonas reinhardtii	growth rate	7.500
Corbicula fluminea	growth	0.840
Daphnia magna	reproduction	2.449
Hyalella azteca	mortality	1.575
Isonychia bicolor	molting	0.160
Oncorhynchus mykiss	mortality	0.546
Pimephales promelas	hatching	0.380
Pseudokirchneriella subcapitata	growth rate / yield	0.100
Salmo trutta	mortality	0.635
Stenonema modestum	molting	1.000
Synechococcus leopoliensis	growth rate	1.870

- Most sensitive endpoint considered per species
- Geomean derived if multiple reliable values per endpoint / species



	Geomean
min (µg/L)	0.100
max (µg/L)	12.54
HC_5 (µg/L) - LogNormal	**0.104 (0.03-0.25)**
HC_5 (µg/L) - BestFit	**0.104 (0.03-0.25)**

AF 3

PNEC = 34.7 ng/L

PMC revision silver PNEC/EQS freshwater (3)

	Taxonomic groups	Species
1	Fish (usually tested species like salmons, bluegill, channel catfish, etc.)	*Salmo trutta* *Oncorhynchus mykiss*
2	A second family in the phylum Chordata (fish, amphibian, etc.)	*Pimephales promelas*
3	A crustacean (e.g. cladoceran, copepod, ostracod, isopod, amphipod, crayfish etc.)	*Daphnia magna* *Ceriodaphnia dubia* *Hyalella azteca*
4	An insect (e.g. mayfly, dragonfly, damselfly, stonefly, caddisfly, mosquito, midge, etc.)	*Stenonema modestum* *Isonychia bicolour* *Chironomus tentans*
5	A family in a phylum other than Arthropoda or Chordata (e.g. Rotifera, Annelida, Mollusca, etc.)	*Corbicula fluminea*
6	A family in any order of insect or any phylum not already represented	*Synechoccus leopoliensis*
7	Algae	*Pseudokirchneriella subcapitata* *Chlamydomonas reinhardtii*
8	Higher plants	/
	Total number of species	**13**

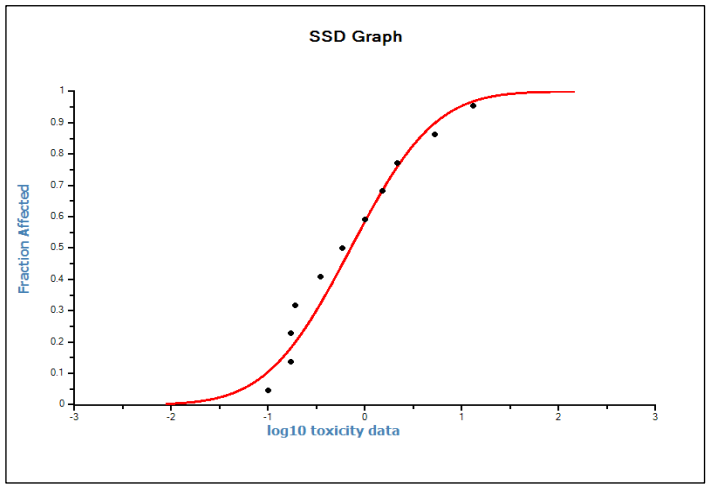
EQS guidance + REACH guidance:

The output from an SSD-based EQS is considered reliable if the database contains preferably more than 15, but at least 10 NOECs/EC10s, from different species covering at least 8 taxonomic groups.

➡ Additional tests proposed (cf. agenda point 2.3)

Sweden revision silver PNEC/EQS freshwater

- **Deterministic derivation** proposed as not enough tax groups
  - Lowest reliable EC_{10}: Schlich et al. (2017)
    - OECD 201 (algae test) with $AgNO_3$
    - EC_{10} for *P. subcapitata* on the endpoints yield and growth rate is 0.10 µg/L (dissolved Ag)
  - AF of 10 → **EQS of 10 ng/L**
- **SSD** also conducted to compare outcome with deterministic derivation (7 tax groups)



HC5 results			
HC5 type	Value	log10(Value)	Description
LL HC5	0,009	-2,062	lower estimate of the HC5
HC5	0,050	-1,300	median estimate of the HC5
UL HC5	0,129	-0,855	upper estimate of the HC5
sprHC5	16,098	1,207	spread of the HC5 estimate

Median HC5: 0.05 µg.L^{-1}
AF of 5 → **EQS of 10 ng/L**

PMC versus Sweden revision silver PNEC/EQS freshwater

Species	Endpoint	NOEC / EC10 (µg/L)	Reference	Sweden NOEC / EC10	Comments
Ceriodaphnia dubia	reproduction	4.360	Kolts et al. 2009 Rodgers et al. 1997 Naddy et al. 2007b	5.230	Sweden considered mortality endpoint and geomean of values derived by RIVM + did not consider Rodgers et al.
Chironomus tentans	growth	12.540	Call et al. 1999	13.000	
Chlamydomonas reinhardtii	growth rate	7.500	Taylor et al. 2016	-	Sweden did not consider study (uncertainties related to methodology)
Corbicula fluminea	growth	0.840	Diamond et al. 1990	1.500	
Daphnia magna	reproduction	2.449	Naddy et al. 2007 Bianchini & Wood 2008 Rodgers et al. 1997 Schlich 2017a	2.140	Sweden considered growth endpoint from Bianchini & Wood
Hyalella azteca	mortality	1.575	Diamond et al. 1990 Rodgers et al. 1997	0.580	Sweden did not consider Rodgers et al.
Isonychia bicolor	mortality	0.160	Diamond et al. 1990	0.170	
Oncorhynchus mykiss	mortality	0.546	Davies et al. 1998 Dethloff et al. 2007	0.170	PMC: geomean Sweden: min value (lowest **hardness**) + did not consider Dethloff et al. (because exp. time shorter)
Pimephales promelas	hatching	0.380	Naddy et al. 2007a	0.350	Sweden considered mortality / growth endpoint and value derived by RIVM
Pseudokirchneriella subcapitata	growth rate / yield	0.100	Schlich 2017b	0.100	
Salmo trutta	mortality	0.635	Davies et al. 1998	0.190	Sweden considered min value (lowest **hardness**)
Stenonema modestum	molting	1.000	Diamond et al. 1992	1.000	
Synechococcus leopoliensis	growth rate	1.870	Taylor et al. 2016	-	Sweden did not consider study (uncertainties related to methodology)

WG Chemicals Ag sub-group discussions

- Currently **insufficient data for SSD**
  - UBA has data available on cyanobacteria and higher aquatic plants (*note*: currently not included in SSD PMC / Sweden) but details on methodology missing
  - In the meantime, UBA confirmed that these data are not reliable
  - PMC indicated they will perform additional tests (cf. agenda point 2.3)
- PMC commented on **discrepancies between SSD dataset PMC / Sweden**; Sweden will check comments and take into account where possible, but if opposite views are identified these will be highlighted for the SCHEER's consideration
- Sweden is checking with COM overall **timeline** for the work expected by the substance subgroups
- Sediment EQS has not been discussed yet

Important notes

1) PNEC will not be < 10 ng/L → even low PNEC does not result in STE score > 1.8 with latest monitoring data…

2) PNEC < 40 ng/L may have impact on ES
   - Site-specific data old → **exposure data / modelling** to be checked
   - Importance of **bioavailability**
   - Budget for 2019 to be included?

2.3 Additional ecotox testing (1)

1) 7d higher plant test (***Lemna minor*** - OECD 221): tax group missing (UBA results not reliable)
2) 72h bluegreen alga test (***Anabaena flos-aquae*** - OECD 201): uncertainty related to existing cyanobacteria tests (UBA + Taylor et al. 2016)
3) 48h rotifer test (***Brachionus calyciflorus*** - ASTM E1440-91): additional tax group

➡ 14-16 species (depending on Taylor et al. study) in 9 tax groups

12 Jan WG call: WG approved performance of additional tests if UBA has no further reliable data on above species

2.3 Additional ecotox testing (2)

- Quotes requested from Ghent University and Fraunhofer
- Costs comparable (**22 k€ - 30 k€**; exact costs depending on analytical technique to be used (ICP-OES or ICP-MS) and total of Ag measurements to be done, which will be decided during the course of testing)
- **Ghent University** selected
  - experience with metals and ecotox tests for metals
  - offer more detailed and test design well justified
  - flexibility to get everything optimally measured/analysed
  - ease of communication
  - timeline
  - non-GLP but planning to publish results (if peer reviewed and accepted in a journal → reliability of results strengthened)
- Tests will be initiated soon (RF next week, final tests April, analysis + reporting May)

coffee break

Precious Metals Consortium

3. Silver reproductive toxicity

3.1 Recap current situation silver reprotox – background (1)

- Ongoing discussions under BPR on **classification of SCAS**
  - SZZ: Repr cat. 1B proposed, cat. 2 agreed
  - SZ, SCZ and SSZHP: Repr cat. 2 proposed
- **Data gap** on reprotox → PMC submitted **TP for EOGRTS** in 2015
- TP now under scrutiny by ECHA → waiting for Draft Decision
- Since 2015: further research published suggesting Ag is reprotox
  - maybe even Repr cat. 1B → Ag restriction for consumer use and banned in EU from electronics, silverware, medical devices, biocidal use, …
  - several weaknesses in recent silver research → data gap still remains, but **update of TP** is necessary
- Even if TP accepted: outcome of EOGRTS is highly unpredictable and risk of classification as Repr cat. 1B still exists!

3.1 Recap current situation silver reprotox – background (2)

Reproductive toxicant	Criteria	Remarks
Category 1A	• Known human reproductive toxicant (development and/or fertility)	• Few substances classified to this level. • Metals: Pb/Pb cmpds
Category 1B	• Mainly based on animal studies • Strong presumption relevance to humans • Evidence must be clear (dev./fert.) • Not secondary i.e. non-specific consequence (including 2^{o} due to marked maternal toxicity, stress etc.)	• **SVHC implications!** • Metals: Cmpds of Co, Cr6+, Ni; metallic Hg
Category 2	• Evidence not sufficiently convincing to assign Cat. 1 • Typically only animal data • Same caveat: should not be a non-specific consequence of other toxicity	• Due to REACH testing increasingly common classification (eventually >1000 substances?)

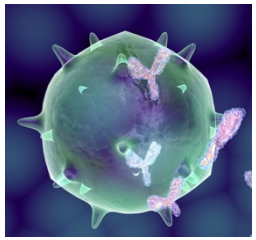
3.1 Recap current situation silver reprotox

Developmental

- Main battleground (*MR view*)
- Pre- & post-natal effects
- Uncertainty: indirect effects, MoA

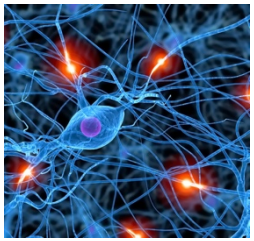
Fertility

- Limited evidence (Sprando study)
- SCAS data (2-gen) no effect



Developmental immunotoxicity

- Babu study
- Indicative not firm evidence
- Weaknesses in study approach



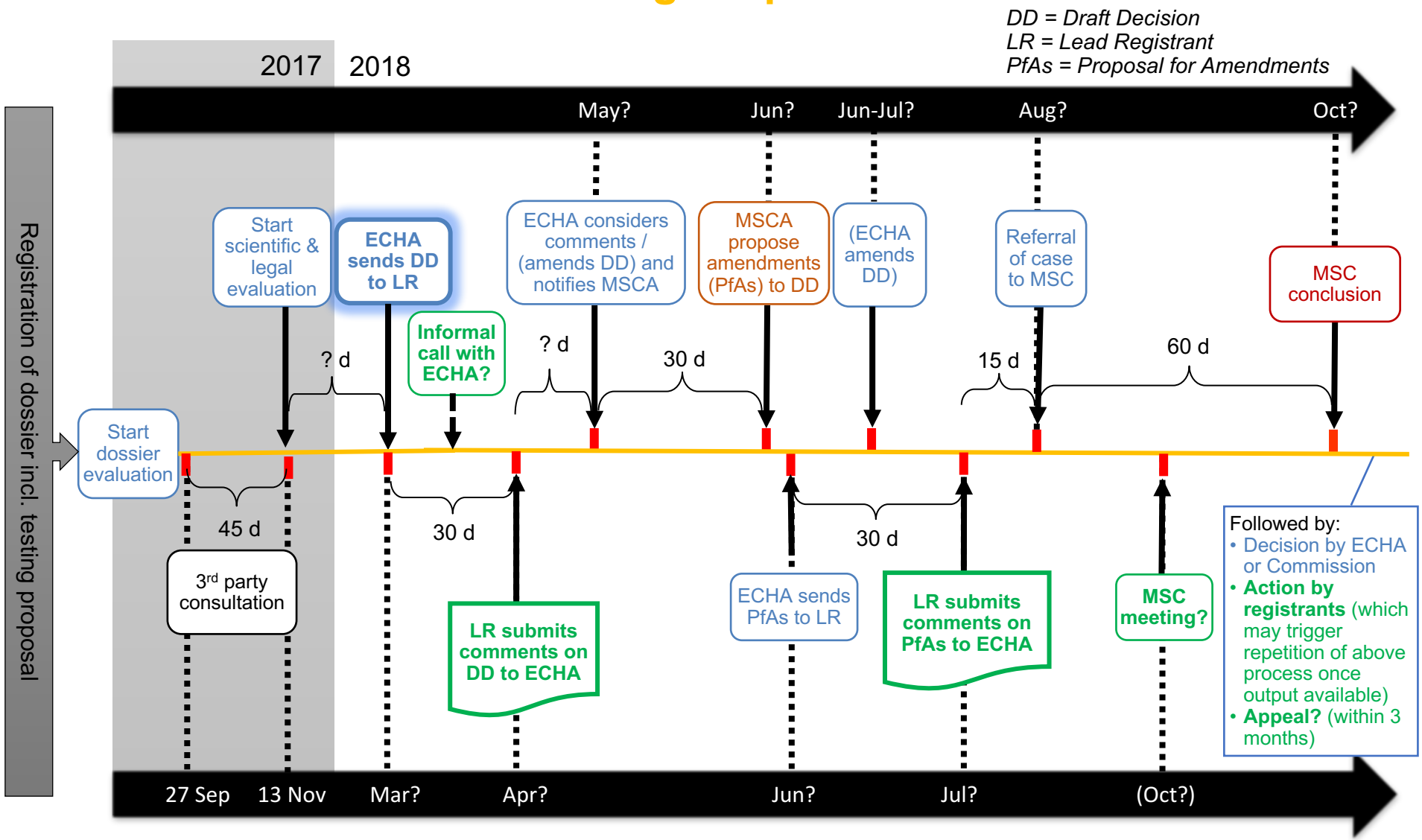
Developmental neurotoxicity

- DNT Ag partial/complex picture
- PMC understood risks to TP
- Ag-Cu axis impact?

3.1 Recap current situation silver reprotox

- Very challenging and chances of industry success finely balanced
- Some weaknesses in Sprando/Babu studies already identified in defence of EOGRTS TP + expert advice gathered
- **MoA** still unclear but might include:
  - Effects on **Cu homeostasis**
  - Indirect effects via **gut microbiome** (maternal / fetal)
  - More speculative possibilities (e.g. generalised stress responses related to indirect reprotox, Ag+ depletion of Se): less likely to be accepted by regulators as true confounders / would take even more experimental effort to build defense case
- **Indirect microbiome effect** (+ data gap at low Ag doses): strongest leverage point for PMC for questioning the outcomes in SCAS / Sprando studies

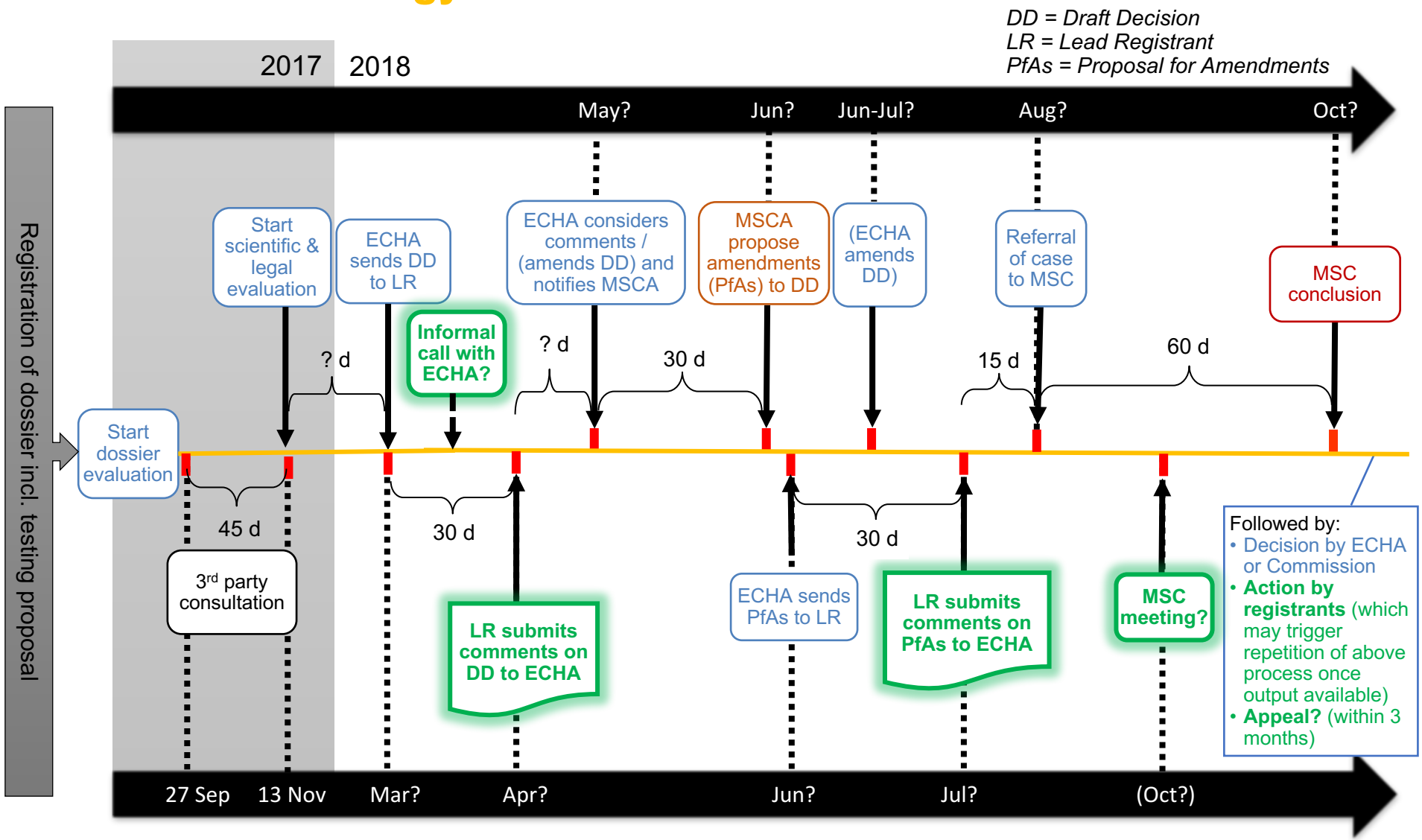
3.2 Status EOGRTS Testing Proposal



3.3 PMC strategy - introduction

- Cf. doc circulated to the WG 1 Feb and updated version in Annex
- Ag: high tonnage and multiple uses
- High regulatory pressure (env. classification, BPR, nano, WFD)
- Recent recognition of Ag as possible reprotox escalates already delicate situation regarding Ag regulatory risk
- **Aim Ag strategy doc**: outline advocacy strategy

3.3 PMC strategy - how to defend TP?



3.3 PMC strategy - immediate actions

- **Review EOGRTS TP** in light of recent publications in literature, and develop best possible science rationale for why it would provide a superior end result to hazard assessment
- Ensure that **strong justification is available for source substance** and read-across approach chosen
- Prepare **defence of TP** by consulting relevant experts and gathering their input to support the need to perform EOGRTS
- Gather justifications to perform **enabling studies** and document the impact on the timing of the overall testing program

3.3 PMC strategy - next actions

- **If high chance to have TP accepted**:
  - Focus on acceptance of study design and timing
  - If needed, trigger discussion at MSC by contacting CARACAL representatives
  - Strategy must be built and adapted during the course of the process
- **If high chance to have the TP rejected**:
  - Prepare for an appeal against the decision (non-preferred option)

3.3 PMC strategy - parallel actions (broader advocacy)

- Development of **mass flow analysis** of silver
- Summary sheet on **socio-economic importance** of silver
- **Stakeholders mapping** including a DUs mapping
  - Sweden (Kemi)?
  - ESTF?

FOR DISCUSSION

- A **DUs communication plan** including key messages on the process

3.3 PMC strategy - Repr classification

- **How to conclude?**
  - Option 1: **EOGRTS rejected**: high risk of Ag classification → still conduct enabling studies which could help to interpret existing data differently
  - Option 2: **EOGRTS accepted** (with modification):
    - Outcome is clear: no classification
    - Outcome is not clear and leads to divergent views → try to avoid cat.1B
    - Outcome is clear: classification as cat.1B
- **How to assess the impact?**
  - EM ongoing work: development of tool to asses regulatory consequences
  - Ag is an example used to test it
  - Outcome will be available early April
- **How to mitigate the impact?**
  - Some DU consequences are difficult to mitigate (e.g. consumer restriction)
  - Consider bioelution testing as a tool to estimate human exposure during use?
  - For industrial and professional uses: develop some shadow RMOAs and some supporting studies (e.g. AoA in some sectors) to defend the best RMMs

3.3 PMC strategy - conclusions

- High nr of unknowns → at this stage very difficult to develop full strategy
- **Layered defence** will be needed: even if EOGRTS TP fails, fall-back of an effective technical defence to mitigate Repr cat.1B classification risk should be ready to deploy, along with a further layer of other advocacy actions
- Strategy outline is designed to help to **prioritize** actions and understand the importance and long-term **consequences** of the reprotox discussions
- **Living document**, to be updated on regular basis to reflect status of the process and related actions needed

3.4 Outcome Tox Expert discussions

23 Nov meeting Holsapple

- Discussion existing reprotox studies Ag
- Defence of and updates to EOGRTS test design discussed (dose-setting, cohorts)
- RAC mindset & case studies discussed
- Ideal final positions PMC could include evidence that:
  - Ag reprotox is a **secondary effect** (preferred outcome), and/or
  - **MoA** is of no / limited relevance to humans (preferred outcome) and/or
  - Ag reprotox is confined to **exposure levels** significantly above those relevant to human RA (less preferred, as this would still mean that soluble Ag is classified as Repr Cat.1B/2 but RA could mitigate)
- Consensus that:
  - Repr cat.1B classification now at bigger risk
  - EOGRTS would address identified weaknesses in existing studies
  - There is suggestive evidence for Ag causing DIT → sufficient trigger for inclusion DIT cohort in EOGRTS
  - **Enabling work is needed**

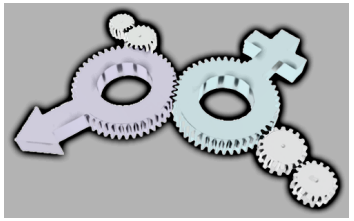
3.4 Outcome Tox Expert discussions: MoA

Includes:

1) Ag+ effects on **Cu homeostasis**

2) Indirect effects via **gut microbiome** (maternal / fetal)
   - considered key theme
   - could offer basis to argue for important indirect effects, incl. Ag DIT
   - suggestion to contact biome expert – prof. Lison (Univ. Louvain)

3) More (speculative) possibilities
   - Generalised **stress responses** related to indirect reprotox
   - Ag+ depletion of Se → consequential **Se micronutrient disorder**
   - Other? (q.v. Ag toxicity recent publications)



3.4 Outcome Tox Expert discussions: stress-test (1)

Argument	Rebuttal possibilities
TP unnecessary – new OGRTS (Sprando et al.) negates need for EOGRTS	• Sprando study protocol weaknesses: e.g. gaps in reproductive organ histopath. and org. wt. data; gaps re fertility parameters • Fertility effects evidence weak / not replicated in 2-gen studies with SCAS • Possibility of 2^{o} toxicity being influential • **New EOGRTS (adapted) would provide precision**
The overall weight-of-evidence for Ag+ reprotox is sufficient	• See also above. • MoA poorly understood / mechanistic relevance to humans not well defined. • Various axes for 2^{o} toxicity not excluded so far, e.g. biocidal impact on microbiome • **New EOGRTS (adapted) could provide better precision**
Latest findings re developmental immunotoxicity (Babu et al.) represent a classification imperative	• The DIT findings in Babu et al., are indicative only and have multiple associated uncertainties (Holsapple opinion) • Key DIT parameters omitted from the study (e.g. TDAR) • Support for DIT postulate weak (adult Ag^{+} immunotox absent or weak evidence / no unique developmental immunotoxicants) • **New EOGRTS with DIT cohort would address**

3.4 Outcome Tox Expert discussions: stress-test (2)

Argument	Rebuttal possibilities
The mammalian toxicity of Ag is understood, and its reprotox profile is explainable	• Mammalian toxicity of Ag^+ is comparatively low (versus some other metals) • But Ag^+ remains a data-poor substance in mechanistic terms • For instance, it is a potent broad-spectrum microbiocide - knowledge still formative stage re linked indirect effects on adult and foetal/neonatal homeostasis (including reproductive / immune systems) • **Enabling/further main studies are required on MoA**
Argyria is of toxicological significance and has been associated with the adverse reprotox findings	• Weight-of-evidence is that argyria is not toxicologically significant and represents adaptive/protective change (q.v. PMC CLH input) • RAC precedent: RAC 35 decision regarding limited significance of argyria • Causal association/correlation between argyria and reprotox has not been robustly demonstrated

3.5 Enabling study gut microbiome: introduction

- **Main objective**: investigate effects of Ag on (parental) gut microbiome of rats at low dose levels (equivalent to those used in Sprando et al.), and in exposure settings that are relevant/directly comparable to planned EOGRTS → strengthen our hypothesis that the silver MoA for reproductive effects includes **indirect effects** via the gut microbiome
- Study would help in EOGRTS design and could provide argumentation to
  1) further **defend our TP** and
  2) **avoid classification** → point stands even if TP is eventually denied! (i.e. study has fallback value even if not directly useful for EOGRTS design)
- Even after DD on TP is issued, we still have chances to defend it (through comments on DD / informal call with ECHA) → proposal / timeline for study useful in discussions with ECHA on timeline needed for EOGRTS
- **20 Feb Mgmt Cttee meeting**:
  - Ag strategy discussed
  - Very unlikely to have results biome study before DD → no rush to start study
- Mail sent to **ECHA** to ask clarity on timing DD → TE agreed to wait for further info before making decision on biome study

3.5 Enabling study gut microbiome: test design

0, 0.4, 4 and 40 mg AgAc/kg/d
n=10/dose/sex

microbiota
homogenization

40 F
40 M

wk 2

wk 3 or 4 (tbd)

serum Ag, Cu, Se
feces Ag

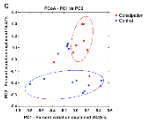
wk 6

serum Ag, Cu, Se
ceruloplasmin
oxidase activity

feces Ag

16s rRNA seq

OTU
Assignment
α- and β-diversity
PCoA, correlation, …



Influence of dietary Ag on the gut microbiota in rats

(S. van den Brule, D. Lison; Feb 2018)

3.5 Enabling study gut microbiome: costs

Quote for the study on the effects of soluble silver on the gut bacterial microbiota

Product or task	Description	Provider	unit price	quantity	total price
Wistar rats	females, 4 weeks, 100-124 g	Janvier	€ 13,61	40	€ 544,40
	males, 4 weeks, 100-124 g	Janvier	€ 13,61	40	€ 544,40
	delivery boxes	Janvier	€ 27,00	14	€ 378,00
	transport	Janvier	€ 125,00	1	€ 125,00
mixing Ag Ac with diet		PMC	€ 1.000,00	1	€ 1.000,00
animal facility	room (price/month)	Animalerie Centrale UCL	€ 249,00	2	€ 498,00
	entry (price/person/month)	2 persons	€ 52,00	4	€ 208,00
	litter	Animalerie Centrale UCL	€ 34,30	3	€ 102,90
	feed	Animalerie Centrale UCL	€ 42,00	2	€ 84,00
Consumables	tubes, tips, ...				€ 2.000,00
QIAamp DNA stool mini kit	50 DNA extractions	Qiagen	€ 272,00	2	€ 544,00
NGS (16S bacterial sequencing)	80 samples (5600 $)	MR DNA lab	€ 56,80	80	€ 4.544,00
	shipping		€ 200,00	1	€ 200,00
ICP-MS (Ag, Cu and Se levels)	in blood (7 or 14 and 28d), feces (7 or 14 and 28d) and intestinal contents (28d)	St Luc	€ 30,00	640	€ 19.200,00
ceruloplasmin activity test	100 tests, in blood (7 or 14 and 28d)	Sigma	€ 469,00	2	€ 938,00
experimental design and data analysis	Sybille van den Brule (month)	UCL	€ 8.000,00	1	€ 8.000,00
NGS data analysis	Jérôme Ambroise (month)	UCL	€ 8.000,00	1	€ 8.000,00
sample collection, DNA exctrations and other assays	Saloua Ibouraadaten (month)	UCL	€ 4.000,00	1	€ 4.000,00
Animal care and exposure	Mihaly Palmai-Pallag (month)	UCL	€ 4.000,00	1	€ 4.000,00
				total	€ 54.910,70
				overhead	€ 10.982,14
				VAT	€ 11.531,25
				TOTAL	**€ 77.424,09**

3.5 Enabling study gut microbiome: timeline

Time schedule		
	weeks	
Test Ag, Cu and Se measurement by ICP-MS	2	
rat acclimation	2	
exposure duration	4	
DNA extraction	1	
Ceruloplsamin activity	1	
Ag, Cu and Se measurement by ICP-MS	2	
mrDNA sequencing	4	
sequencing analysis	4	
overall analysis	2	
total	22	**5 months**

- **+ lead time of min. 2 months** (for ordering rats, food, development Ag analysis...)
- Most critical aspect: **ICP-MS measurement** of Ag in biological tissues which might require significant development

3.5 Enabling study gut microbiome: pros/cons

Pros	Cons
Objective experimental evidence that Ag impacts the biome at lower Ag concentrations supports PMC hypothesis of indirect effects and might **avoid Repr 1B classification** (and result in Repr 2?) → point stands even if EOGRTS TP is eventually denied!	Only **supportive evidence**: difficult to exclude that biome effects and reprotox effects appear at the same dose but independently / difficult to prove that reprotox effects are secondary to biome effects
'Simpler' to test than other suggested (indirect) MoAs	Study will still take ~ 1/2 year
Biome uncertainty also important to **EOGRTS TP defence** (otherwise we depend solely on already identified weaknesses in Sprando/Babu studies) → PMC in stronger position if we can say efforts via enabling study are already underway (and final decision on EOGRTS design should await outcome study)	Results will not be available in time for the update of the EOGRTS TP → **business risk** that PMC embark on the biome study, but in the meantime lose the TP argument and EOGRTS is denied
Results will support **EOGRTS study design** (because current data gap for a key EOGRTS dose-setting parameter)	

3.6 Status CLH proposals silver active substances (SCAS)

- 3 further CLH proposals submitted by Kemi (Sweden) for SCAS under the BPR
- **Silver zeolite** (SZ) and **Silver copper zeolite** (SCZ):
  - **Repr 2 classification**: no substance-specific data available but classification based on studies with SZZ, AgCl (Shavlovski paper) and AgAc (Price & George 2002 study and 2017 study from Sprando et al.) → conservative approach using same classification as SZZ (given structural similarity with SZZ and similarity of effects observed with other Ag salts that do not contain Zn)
  - **Env classification**: Aq. acute 1 and Aq. chronic 1: similar approach to SZZ
- **Silver sodium zirconium hydrogen phosphate** (SSZHP):
  - **No Repr classification:** 2-gen study with SSZHP available that 'did not result in effects meeting criteria for classification'
  - **Env classification**: Aq. acute 1 and Aq. chronic 1: similar approach to SZZ
- Awaiting 60 d public consultation
- Expert input for PMC comments collected; comments will be drafted and sent for review once public consultation has started

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4. Budget

2019 Budget

1. Ag metal (including nano)	137.071 €
1.1 REACH registration	0 €
1.2 REACH dossier maintenance	21.000 €
1.3 REACH evaluation	0 €
1.4 REACH classification & labelling	10.000 €
1.5 REACH authorisation	0 €
1.6 Internal and external fixed Scientific Managers	94.214 €
1.7 IUCLID IT hosting system	476 €
1.8 Knowledge Management tool + hosting	905 €
1.9 SIEF communication tool	476 €
1.10 Science budget	10.000 €
2. Ag compounds	**178.071 €**
2.1 REACH registration	0 €
2.2 REACH dossier maintenance	62.000 €
2.3 REACH evaluation	0 €
2.4 REACH classification & labelling	10.000 €
2.5 REACH authorisation	0 €
2.6 Internal and external fixed Scientific Managers	94.214 €
2.7 IUCLID IT hosting system	476 €
2.8 Knowledge Management tool + hosting	905 €
2.9 SIEF communication tool	476 €
2.10 Science budget	10.000 €

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5. AOB, next meetings/calls and closing remarks

Next Ag WG meeting:

- **9, 10 or 11 Oct 2018**

THANK YOU

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