Precious Metals Consortium

Precious Metals & Rhenium Consortium

Silver Work Group Meeting

19 October 2017 | Brussels

Precious Metals Consortium

1. Welcome and introduction

Rob Garrett (Ames, United Kingdom)

1.1 Reminder on confidentiality and competition law

Attendees should refrain from any discussion on pricing, market shares and volumes and other information that could be considered as market sensitive and covered by antitrust legislation

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
2. Substance Evaluation (SEv) by Dutch MSCA
   - 2.1 Final results testing and data collection uses nanosilver (dossier update)
   - 2.2 Further process
3. Water Framework Directive (WFD) prioritisation
   - 3.1 Status process and timeline
   - 3.2 Status revision silver PNEC / EQS

LUNCH

4. CLH proposals silver active substances (SCAS)
   - 4.1 Proposed CLH for SZ, SCZ, SSZHP
   - 4.2 PMC commenting
5. Testing proposal EOGRTS
   - 5.1 Status current knowledge silver reproductive toxicity
   - 5.2 Need for revision testing proposal / study design ?
   - 5.3 Need for enabling studies before EOGRTS ?
6. Workplan and budget
7. AOB, next meetings/calls and closing remarks

FOR APPROVAL

1.4 Approval of the minutes of the last meeting (23 March 2017) and status of action points

	What?	Who?	Status
Substance Evaluation			
1	Follow-up dissolution rate testing in aquatic ecotox test media and possible reasons for Ag loss / precipitation as suggested during the meeting	ARCHE	Done
2	Follow-up soil ecotox test and dissolution rate testing in soil as suggested during the meeting	WCA	Done
3	Contact Martin Scholze for statistical analysis results definitive ecotox tests	PMC Sec	Not needed
4	Organise call with WG to discuss results from the soil dissolution rate test and soil porewater DOC measurements	PMC Sec	Done
5	Urge downstream users to provide input to the nanoAg use questionnaire	NanoAg registrants	Done
6	Phys-chem / ecotox test reports review	PMC Sec + Ag WG	Done
7	Organise call / meeting with RIVM to discuss results	PMC Sec (+ WCA + ARCHE)	Done
8	Organise call with WG to discuss need for further fate testing	PMC Sec	Not needed
9	Include phys-chem / ecotox / use data in Ag dossier	PMC Sec / WCA / ARCHE	Done
Water Framework Directive (WFD) prioritisation			
10	Participate in discussions Ag specific sub-group for review of PS list and WL	PMC Sec	Ongoing
11	Build ecotox dataset for possible revision Ag REACH PNEC	PMC Sec	
CLH proposal silver containing active substances (SCAS)			
12	Follow-up CLH proposals SCAS	PMC Sec	Ongoing
13	Check learning lessons ECI on CLH (e.g. actual active substance / precursor)	PMC Sec with ECI	

APPROVAL OF DRAFT MINUTES?

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2. Substance Evaluation (SEv) by Dutch MSCA

2.1 Final results testing and data collection uses nanosilver (dossier update)

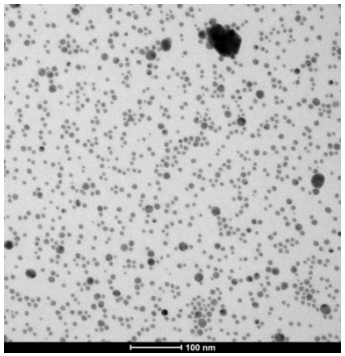
- **Final decision** 6 Jul 2016: further information required to clarify initial concerns:
  1. Comparison of **ecotoxicity** smallest Ag nanoform ('nanoAg') registered / ionic silver (as $AgNO_3$)
     - Algae (OECD 201)
     - Daphnia (OECD 211)
     - Soil microorganisms (OECD 216)

     \+ **phys-chem** characterisation of tested form (incl. T/D)
  2. Information on **fate** of nanoAg in soil pore water and the soil solid fraction **only** in case info in Request 1 indicates toxicity nanoAg > ionic Ag in at least one toxicity test
  3. Information on the **uses** for each individual nanoform registered

- **Timing** split: 12 months if soil fate testing (13 Jul 2017) not needed and 30 months if soil fate testing needed (14 Jan 2019)

Final results testing and data collection uses nanosilver (dossier update)

Phys-chem characterisation nanoAg – basic properties



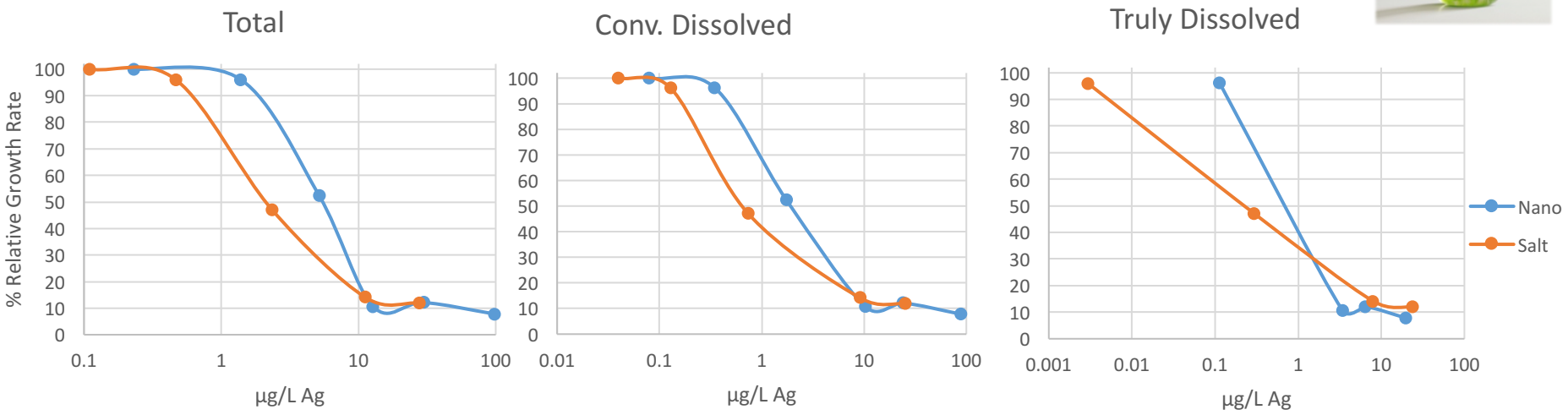
- Aqueous nanosilver suspension, 37% Ag
- **Granulometry** (TEM / DLS)
  - Mainly single primary particles
  - Relatively homogeneous size/shape
  - Spherical
  - Mean primary particle size = **9.4 nm**
- **Volume specific surface area** (VSSA) calculated based on theoretical model, using results of density and PSD measurements
- Info on **surface treating agent** (confidential) provided by manufacturer
- **Density** determined according to OECD 109
- Point of zero charge / isoelectric point (IEP) / point of zero zeta potential determined by ELS

Final results testing and data collection uses nanosilver (dossier update)

Ecotoxicity testing nanoAg vs $AgNO_3$ (1)

- Direct comparison of EC_x values from (as far as possible) identical tests
- If nanoAg displays 'greater toxicity' than ionic silver in any of the tests, then additional testing of fate of nanoAg in soil required
- **Algae** growth inhibition test - OECD 201

Growth rate response curve 0-72 hrs



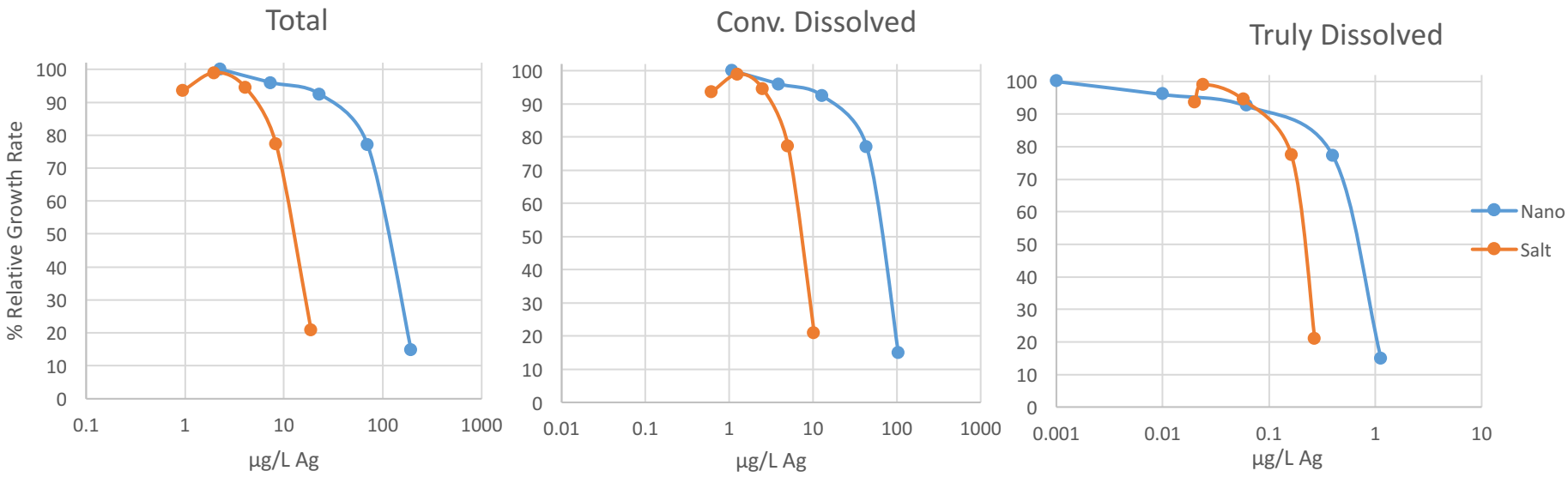
→ In all silver fractions, silver nitrate is more toxic than nanosilver

Final results testing and data collection uses nanosilver (dossier update)

Ecotoxicity testing nanoAg vs $AgNO_3$ (2)

- ***Daphnia magna*** reproduction test - OECD 211

Reproduction response curve 0-21d



→ In all silver fractions, silver nitrate is more toxic than nanosilver

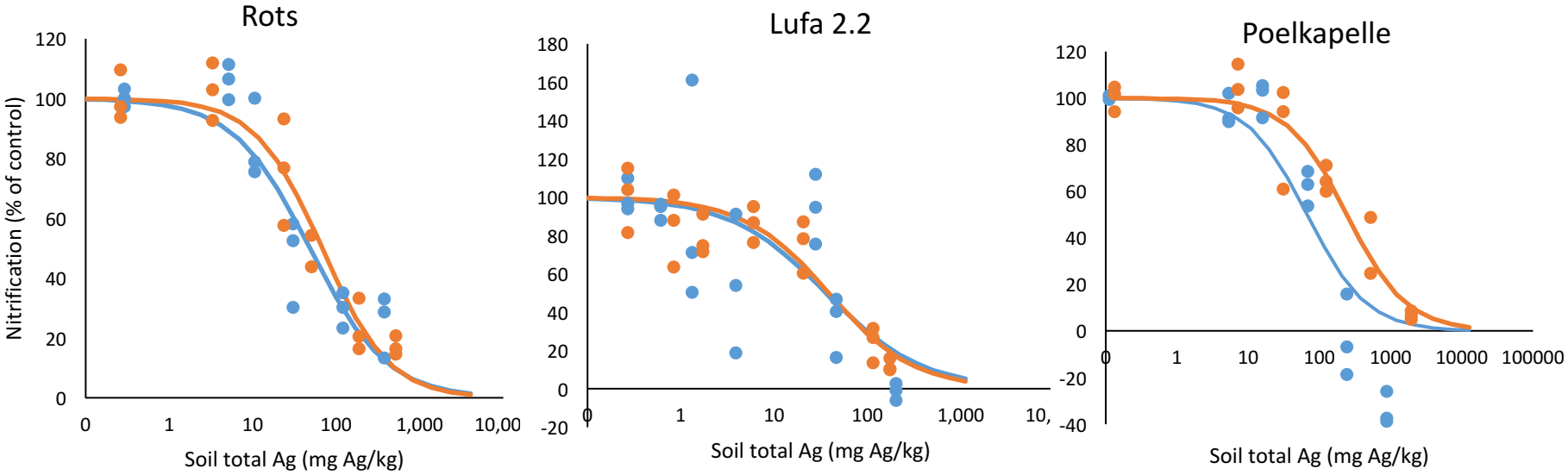
Final results testing and data collection uses nanosilver (dossier update)

Ecotoxicity testing nanoAg vs $AgNO_3$ (3)

- **Soil microorganisms** nitrification test - OECD 216

PNR 0-14d

- **Nanosilver**
- **Silver nitrate**



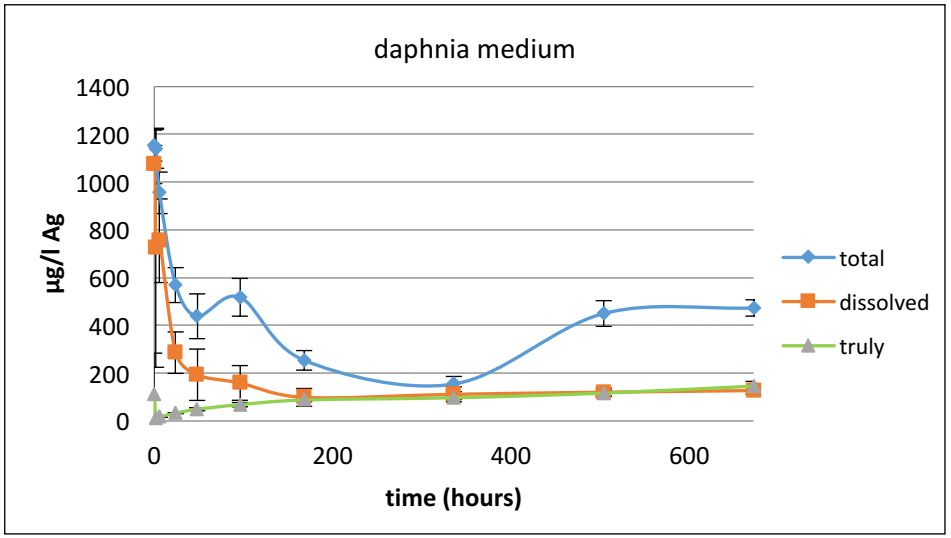
→ In 1 soil, silver nitrate is more toxic than nanosilver

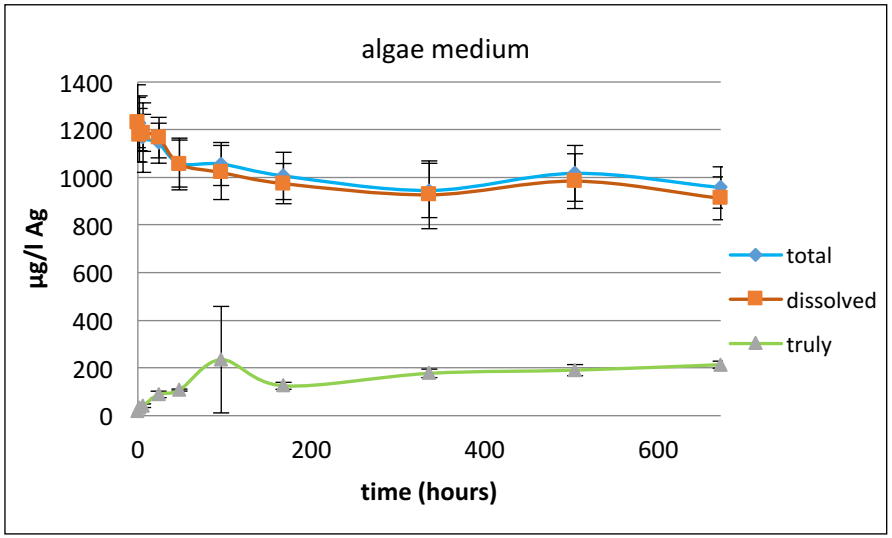
→ In 2 other soils no significant difference

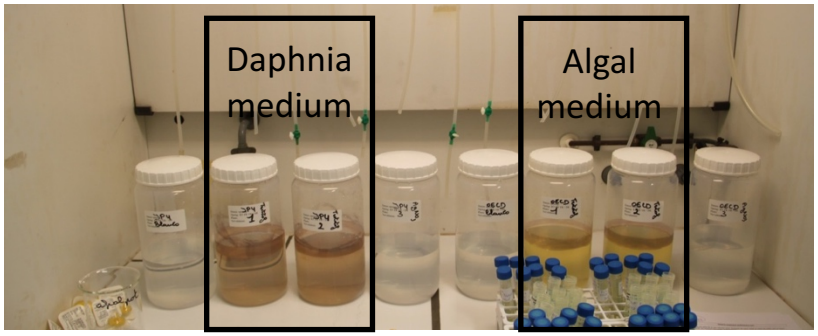
Final results testing and data collection uses nanosilver (dossier update)

Phys-chem characterisation nanoAg – T/D (1)

- Dissolution rate in aquatic test media



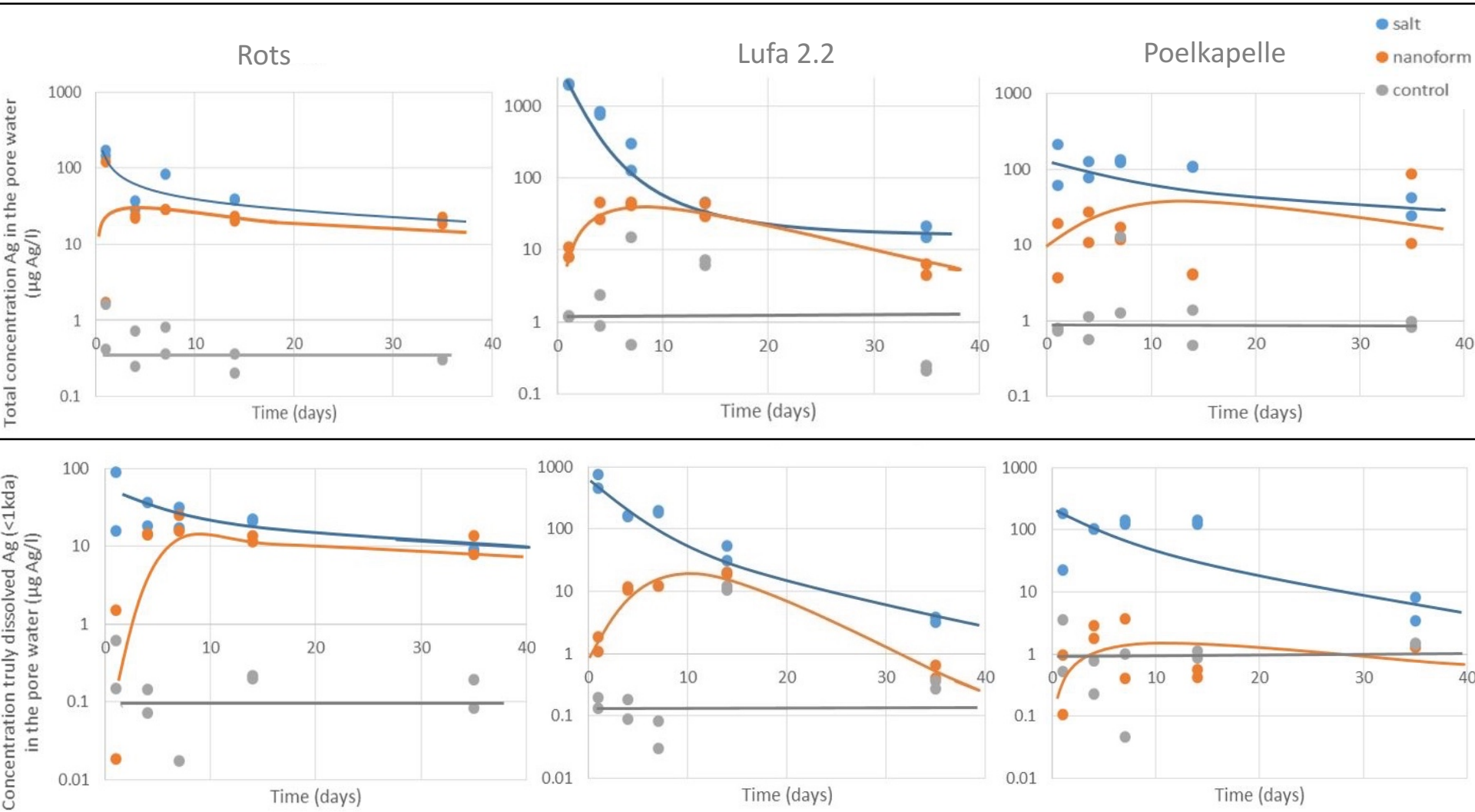




Final results testing and data collection uses nanosilver (dossier update)

Phys-chem characterisation nanoAg – T/D (2)

- Dissolution rate in soil



Final results testing and data collection uses nanosilver (dossier update)

Information on uses

- Only 2 forms of nanoAg currently registered under REACH, < 3 t/a
- **Use questionnaire** sent to both nanosilver registrants and their downstream users
- Based on feedback received, one industrial use and 2 ES for nanosilver included in the dossier:
    1) Manufacture of nanosilver
    2) Use of nanosilver at industrial site in sintering processes for production of electronics
- No nanosilver present in the end product (transformed to ‘bulk’ silver layer): further service life covered with existing ES for Ag as the form is not nano anymore
- Limited release to environment

2.2 Further process

- All results testing / data collection included in Ag dossier and submitted by LR and 2 co-registrants by **13 July**
- In addition to gathering information on uses of the two nanoAg forms, ongoing parallel review of uses of Ag and Ag compounds *(unrelated to SEv)*
- Meeting eMSCA 22 May:

	What	When
1	Requests 1 & 3 of decision	13 July 2017
2	Requests 1, 2 & 3 of decision	14 January 2019

  - **eMSCA has 12 months to evaluate new information** (until 13 July 2018)

	Possible conclusion	eMSCA action
1	No further data needed	Submission of 'conclusion doc' to ECHA
2	Further info needed to address concern	New Draft Decision (incl. soil fate testing?)

  - Once the SEv is finalised, the eMSCA will conclude on how to continue with the concern (e.g. C&L, restriction, authorisation, or other)

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3. Water Framework Directive (WFD) prioritisation

3.1 Status process and timeline (1)

- **Monitoring based exercise**: silver mentioned in short list of substances under further consideration for EQS derivation

- 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**

Status process and timeline (2)

- Draft **WL report** JRC: silver not proposed for WL

*"**Silver**, omethoate, selenium and the pyrethroids were identified as having a **low/medium amount of monitoring data** in the prioritisation. Silver, omethoate and selenium are not proposed as WL substances. According to the latest information available at the moment, dated 2014 , silver, omethoate and selenium (in water) are **RBSPs in a significant number of MS** (resp. 7, 6 and 10 MSs). **This tends to support the idea of an EU-wide risk.** In addition, more monitoring data should become available via routine monitoring in the future, in particular for silver and omethoate. What's more, the additional monitoring data recently gathered combined with the data previously used in the prioritisation now show more than 2000 samples in more than 100 sites and 4 MS for silver in the dissolved fraction, so it fulfils the minimum requirements for the number of MS, sites and samples used under the previous prioritisation."*

- **Silver specific sub-group**
  - **Sweden** (lead), Germany, Latvia, Denmark, **France**, EM & PMC
  - Agree on EQS before end 2017 (!) for all matrices that could be of relevance (!!), including sediment
  - Starting point: JRC report
  - Sweden is compiling list of available studies (REACH, RIVM Ag ERL report, BPR)
  - PMC (re-)assessing ecotox dataset

Process and timeline: concerns (1)

- Clear timeline / process from Commission's side still lacking...
  but preparatory work continuing

  *"The **timetable** presented to the WG Chemicals in March was aiming at a dossier to be presented to the **SCHEER** very early in 2018, with an expected 4 more months to get the SCHEER opinion and 2 months to include their comments (these last estimates on the SCHEER consultation based on previous EQS derivation). The aim was then for the JRC to recalculate if needed the STE score so that we could discuss the EU-wide relevance of the substance on this basis at the WG Chem meeting that would probably take place around Oct 2018. The rationale behind this is to have in the course of 2018 a **harmonised EQS** for these substances and also an indication of the EU-wide relevance of the substance, in time for MS to consider them in their pressures and impact assessments to be finalised in 2019, and then in their reviews of their **RBSP** for the third cycle."*

Process and timeline: concerns (2)

- Never received an update on the **monitoring data** availability for silver
  - Will be presented at next WG Chemicals meeting
- **Substance-specific sub-group** set up with almost 6 months delay
- '**Harmonised EQS**' in the course of 2018 → harmonised = set by EU legislation
  - EQS developed within CIS process, to be used by MS at national level
  - SCHEER review?
- **EC call for tenders** "Water pollutant quality standards and monitoring" refers to ongoing review PS list & WL; 'number of substances' under consideration for EQS derivation
  - Silver included?
  - How will work be aligned with work by substance-specific sub-groups?

➡ **Letter to Commission to request clarity, co-signed by EM**

Next **WG Chemicals** meeting: 26-27 Oct 2017

3.2 Status revision silver PNEC/EQS – Freshwater (1)

Sweden:

- First call 5 Sep; next call 20 Oct to discuss timeline
- Look at REACH + RIVM (+ BPR data + recent studies)
- Likely not sufficient taxonomic groups to apply SSD
- 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)
- Assessment factor of 10?

3.2 Status revision silver PNEC/EQS – Freshwater (1)

PMC:

- Also (re-)assessing data
- **Selection criteria** in line with MERAG criteria and also RIVM criteria, except for:
  1) Dissolved Ag concentrations only
     - Dissolved Ag concentrations preferred but also look at data as **total Ag concentrations** - only in case tests are performed in reconstituted or tapwater (with low SS)
  2) Low **DOC**
     - Selection of DOC as a criterion implicitly suggests that DOC influences chronic Ag toxicity towards freshwater organisms
     - Following this reasoning, derivation of location/river specific EQS values for Ag should therefore incorporate a DOC correction
- Some data previously considered for PNEC not valid (nominal values)
- Still sufficient taxonomic groups to apply SSD (because of new data)
- Assessment available for internal review by early Nov

Status revision silver PNEC/EQS – Freshwater (2)

- Take also studies on **nanoAg** into account?
  - Preferred option: focus on studies with soluble Ag salts and use nanoAg studies as supportive data
  - If no data on Ag salt for specific species available: consider nanoAg studies but only in case values are measured and for dissolved Ag

- Next step – **bioavailability**?
  - Toxic effects of Ag(I) may change if present primarily as a dissolved complex rather than a free (hydrated) cation
  - In general, Ag less toxic to freshwater aquatic organisms under conditions of low dissolved Ag ion concentration and increasing water pH, hardness, sulfides, and dissolved and particulate organic loadings
  - Recent studies indicate importance of sulfide as a ligand, even in fully oxygenated aquatic systems
  - Knowledge of Ag speciation and its consequent bioavailability is crucial to understanding potential risk

Status revision silver PNEC/EQS – Sediment (1)

- **Sweden**:
  - No sediment EQS proposed yet
  - Look at REACH + BPR data

- **JRC** report:

  $AA\text{-}QS_{freshwater,\ sed}$: 1.2 mg/kg dw for *Hyalella azteca* (10 d / NOEC 12 mg/kg dw)

- Overview sediment PNECs:

Stakeholder	$PNEC_{sed}$	Comments
UK EA	1.2 mg/kg dw	Based on 10d test with *H. azteca* and AF of 10
PMC	438 mg/kg dw	Based on 10d test with *H. azteca* and AF of 10 + PNEC normalized to a sediment with a 5% OC content
ESTF	9.58 µg/kg ww	Based on 28d test with *Lumbriculus variegatus* and AF of 10; calculated as $PNEC_{suspended\ solids}$

!

Status revision silver PNEC/EQS – Sediment (2)

- **UK EA $PNEC_{sed}$**:
  - Based on 10d test with *H. azteca* (Call et al., 2006):
    - $AgNO_3$ spiked into 2 natural lake sediments with low binding capacity (TOC < 1 %, AVS < 1.1 µmol/g dw)
    - flow-through test design
    - 7d equilibration
    - $NOEC_{growth}$ = 12 mg Ag/kg dw (nominal)
    - AF 10 → **$PNEC_{sed}$ = 1.2 mg Ag/kg dw**
  - Comments:
    1) 10d = **acute** exposure → should not be used to derive long term PNEC
    2) Sediment concentrations not measured → **nominal** values

Status revision silver PNEC/EQS – Sediment (3)

- **PMC $PNEC_{sed}$**:
  - Based on 10d test with *H. azteca* (Call et al., 2006)
  - PNEC further normalized to a reference sediment with 5% OC
    - Response of *H. azteca* and *C. tentans* demonstrated clear relationship between OC & NOEC (normalization equation restricted to *H. azteca* data)
    - Default OC conc. EUSES (5%) used to set final PNEC → **$PNEC_{sed}$ (5 % OC) = 438.13 mg Ag/kg dw**
  - Comments:
    1) 10d = **acute** exposure → should not be used to derive long term PNEC
    2) Sediment concentrations not measured → **nominal** values
    3) **OC normalization** equation based on only 3 data points:

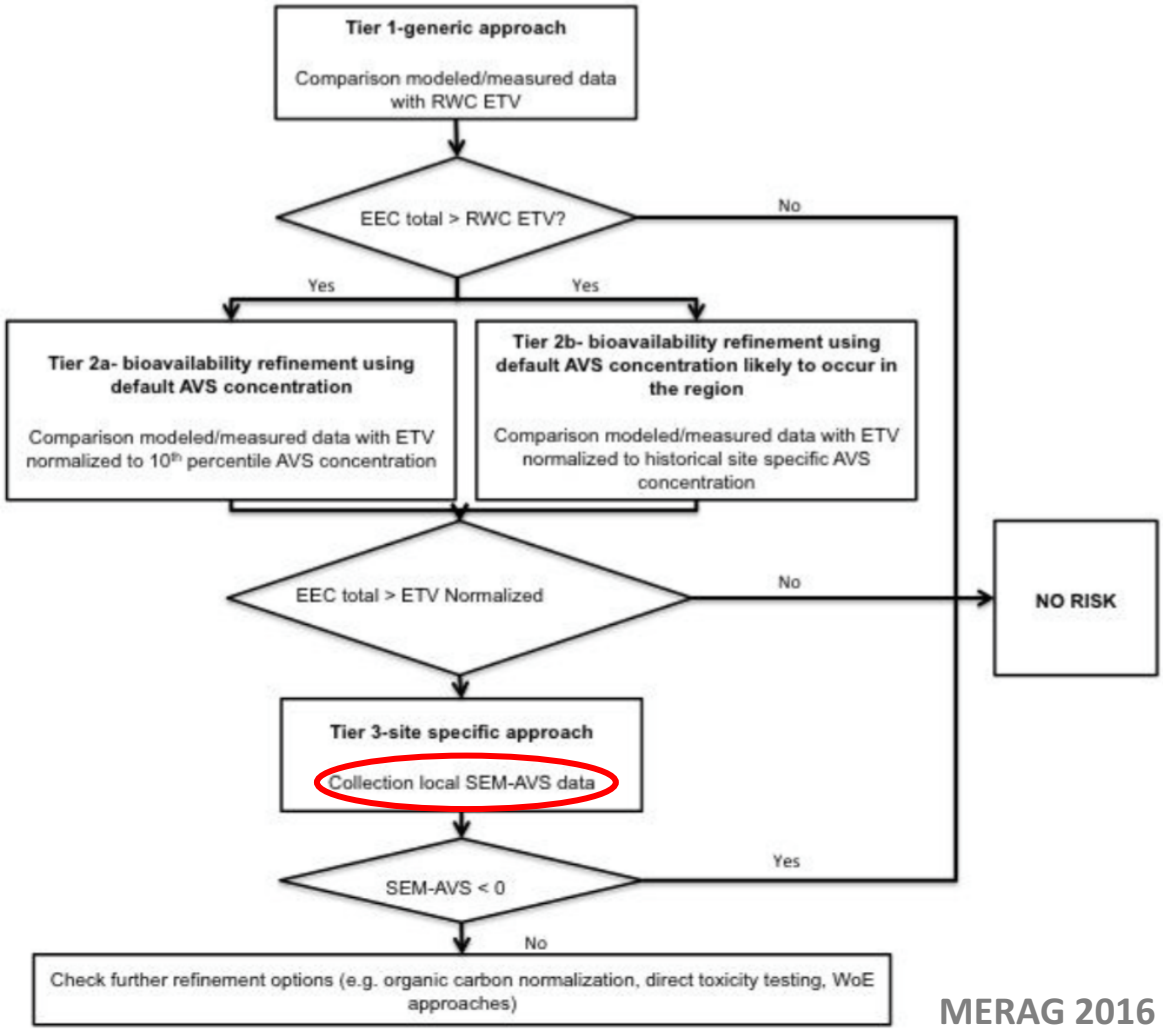
Study	Test substance	OC content	NOEC *H. azteca*	Comments
Call et al. (2006)	$AgNO_3$	0.29 %	12 mg Ag/kg dw	
	$AgNO_3$	2.5 %	2150 mg Ag/kg dw	Other sediment parameters (clay / Fe / AVS conc.) also >>
Hirsch (1998)	Ag_2S	1.63 %	> 753.3 mg Ag/kg dw	Ag_2S very insoluble

Status revision silver PNEC/EQS – Sediment (4)

- **ESTF $PNEC_{sed}$**:
  - Based on 28d test with *L. variegatus*:
    - Ag_2SO_4 spiked into artificial OECD sediment with no AVS and ± 2% OC content
    - static test design
    - 48h equilibration
    - $NOEC_{growth}$ = 0.332 mg Ag/kg ww (0.441 mg Ag/kg dw), AF 10
    - PEC calculated for freshly deposited particulate matter → NOEC transformed to reflect freshly deposited matter (lower density & lower fraction of solids) → **$PNEC_{suspended\ solids}$ = 9.6 µg Ag/kg dw**
  - Comments:
    1) **$PNEC_{suspended\ solids}$** should not be used for comparison with truly measured Ag concentrations in sediments
    2) Short equilibration time (48h) → **toxicity caused via overlying water?** (4.4-12.7 µg Ag/L at end of test) (OECD: equilibration time 48h-7d but for metals in general long equilibration times needed)
    3) Rajala et al., 2016: *L. variegatus* study on toxicity of nanoAg / $AgNO_3$ in artificial and natural sediments (2 lake sediments) → Ag more toxic in artificial sediment than in natural sediments → importance of taking **bioavailability** into account

Status revision silver PNEC/EQS – Sediment (5)

- **SEM-AVS model**:
  - Bioavailability assessment model
  - **SEM** = Simultaneously Extracted Metals; **AVS** = Acid Volatile Sulfides
  - Already used in several EU RAs (Cu, Cd, Pb, Ni, Zn) to address inherent fundamental deficiencies of dry- or wet weight assessment approaches
  - Ag very high affinity to bind with sulphides
  - Berry et al. (1999): **AVS** predominantly controlled Ag toxicity in sediments for marine amphipod *Ampelisca abdita*



MERAG 2016

Status revision silver PNEC/EQS – Sediment (6)

Sweden to propose ESTF $PNEC_{sed}$?

Option		Pros	Cons
1	Accept **ESTF $PNEC_{sed}$** (absence of other chronic studies) and try to get **SEM-AVS** approach accepted	• No additional testing • SEM-AVS is valid, scientifically justified approach	• ESTF study flawed; overly conservative PNEC • RCRs >> 1 in the REACH ES! • No guarantee that SEM-AVS approach will be accepted for Ag
2	Challenge ESTF study and suggest **REACH $PNEC_{sed}$** instead	• No additional testing	• PNEC based on acute study + nominal values • OC normalisation scientifically not justifiable
3	Challenge ESTF study and suggest **UK EA $PNEC_{sed}$** instead	• No additional testing • No need to justify OC normalisation	• PNEC based on acute study + nominal values
4	Challenge ESTF study (suggest UK EA $PNEC_{sed}$ as provisional) and address data gap with **well-designed sediment tests** (long term, 3 species, natural sediments low in AVS/OC)	**Only scientifically robust option** **Recommended by Ag EQS sub-assembly**	Additional testing / cost: • 100-150 k€ for 3 tests


LUNCH
BREAK

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4. CLH proposals silver active substances (SCAS)

4.1 Proposed CLH for 3 SCAS (1)

- 3 further CLH proposals submitted by Kemi (Sweden) for SCAS under the BPR:
  - silver zeolite (SZ)
  - silver copper zeolite (SCZ)
  - silver sodium zirconium hydrogen phosphate (SSZHP)

- **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 Ag acetate (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**: Aquatic acute 1 and Aquatic 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**: Aquatic acute 1 and Aquatic chronic 1: similar approach to SZZ

Proposed CLH for 3 SCAS (2)

- **Human health classifications**:
  - RAC conclusions on SZZ taken into account, in addition to substance-specific data where available and more recent Ag data
  - Proposed classifications for these 3 SCAS favourable to the original proposed classification of SZZ and the achieved result seems largely carried over

- **Environmental classifications**: same error has been made as for SZZ not fully recognizing the metals classification scheme

- 45d public commenting to start soon?

4.2 PMC commenting

- **Human health classifications**: comments on **Repr** classification SZ and SCZ:
  - Mostly based on same papers/studies as SZZ Repr classification → **re-iterate earlier PMC comments** focusing on the toxicity of the zeolite moiety and the indirect influence of the Cu homeostasis disruption
  - Add commentary on **Sprando et al.** study:
    - Kemi's misconception that argyria is adverse effect
    - View of study's severity outcome
    - Deficits in relation to EOGRTS
    - Study (still) does not inform on mode of action → important data gap
  - Taking into account established position on SZZ (Repr 2) and more recent Ag data: no strong arguments against CLH Repr proposals BUT existing studies do not cover the mode of action → covered by **EOGRTS** Testing Proposal
- **Environmental classifications**: **re-iterate earlier PMC comments**

➡ Comments will be drafted and sent for review once public consultation has started

Further info

- **ESTF:**
  - Intentions not clear, depending on members (meeting 24 Oct)
  - Will not fight read-across arguments related to SZZ and the applicability of the 2-gen study to other SCAS which contain zeolites → would lead to data gap
  - Sprando et al. study included in BPR dossier on request of Kemi

- **Kemi**:
  - Have not started review elemental Ag yet
  - EPMF approached by company preparing BPR dossier elemental Ag → inclusion REACH data?
  - Possibility for another meeting with Kemi early 2018?

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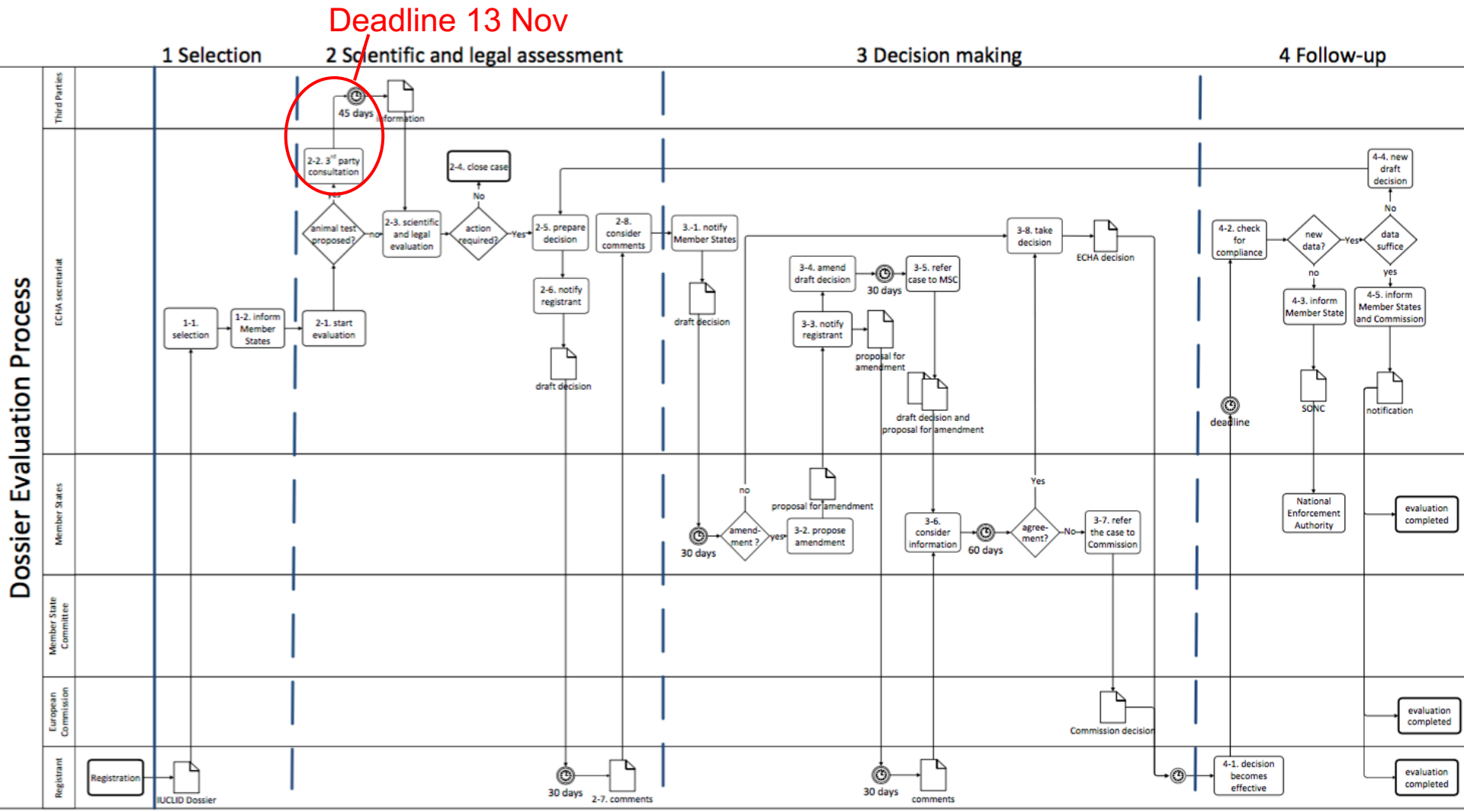
5. Testing proposal EOGRTS

Dossier evaluation process



Ag Reproductive toxicity: Headlines

Notable shifts in position over last 2 years

- **SCAS CLH outcome:** ECHA RAC precedent ▶ classification of Silver Zinc Zeolite Repr Cat. 2. RAC mainly attribute effects to Ag^+

- **More data emerging on SCAS:** Further 2-generation reproductive toxicity study data. Developmental effects a focal point

- **Two new & important publications (2016/17):** US FDA OGRTS on Ag^+ (Ag acetate). Includes new developmental immunotoxicity data

- **Overall balance of evidence:** Shifted adversely

Ag Reproductive toxicity: Headlines

Breakdown of big picture for Ag WG consideration

Platform for your business decision-making

Good news 

Bad news 

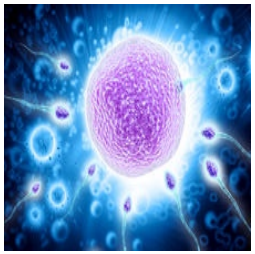
Equivocal / Unclear 

Data gap 

Reproductive toxicity – Key aspects / Testing

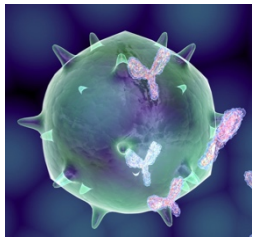
Developmental

- Pre- and post-natal stage
- Embryo-/fetal & pup development
- Includes teratogenicity



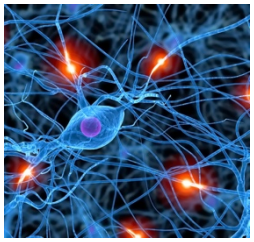
Fertility

- Reproductive performance
- Reprod. organs: weight, pathology, sperm parameters etc.



Developmental immunotoxicity

- Sensitivity of formative system
- Functional testing as well as evaluating lymphoid tissues



Developmental neurotoxicity

- Sensitivity of neonatal CNS
- Endocrine linked aspects

Classification for reproductive toxicity

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?)

Ag^+ Developmental toxicity [1]

Prior position

- Absence malformations in offspring (teratogenicity)

- Short-term developmental toxicity: (Shavlovski study) but query high doses/methodology & offset by 'clean' NTP study

- 2-gen studies SCAS: Moderate developmental effects, e.g. with SZZ. RAC did assign Cat. 2 (Ag^+ effects their focus)

- Mitigation: SCAS not ideal read-across. Query indirect effects Ag (e.g. gut microbiome). Debate over MoA relevance

Conclusion: Was already finely balanced. But possibilities re counter-arguments & rescue via well-designed EOGRTS

Ag^+ Developmental toxicity [2]

Food and Chemical Toxicology 106 (2017) 547–557

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Silver acetate exposure: Effects on reproduction and post natal development☆

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ABSTRACT

Effects of oral silver acetate exposure were assessed in P generation and F generation post-natal day 26 rats. Male and female Sprague Dawley rats (n = 20 each) were exposed to silver acetate at 0.4, 4.0 or 40.0 mg/kg bw in their drinking water for 10 weeks prior to and during mating. Females were exposed to silver acetate throughout gestation and lactation. Clinical signs, body weight, feed and fluid consumption were recorded regularly. Decreased mean daily fluid consumption was observed in male and female animals during the 10 week pre mating period and during gestation in the 40 mg/kg bw dose group. Decreased fertility was observed in the 40 mg/kg bw dose group. Decreased feed consumption was observed across all dose groups and decreased mean daily fluid consumption was observed in the 4.0 mg/kg dose group during lactation. Decreased implant numbers, mean numbers of pups born/litter and numbers of live pups born/litter was observed in the 40 mg/kg bw dose group. Pup weight was reduced on lactation days 0, 4 and 7 (males) and 4, 7 and 21 (females) in the 4.0 mg/kg bw dose group and in males at lactation day 21 (40 mg/kg bw dose group). Runting was observed in males (Lactation Day; LD 4) and female (LD 4 and 7) animals in the 4.0 mg/kg bw dose group. Reduced postnatal-day 26 pup weight was observed in male pups in the 40 mg/kg bw dose group and female pups in the 4.0 mg/kg bw dose group.

Published by Elsevier Ltd.

US FDA

- New OGRTS on AgAc
- Credible research team
- 2017 publication

Ag^+ Developmental toxicity [3]

New

- Sprando study: Developmental toxicity (↓ nr implants; ↑ pup mortality; ↑ incidence of runts/F1 delayed growth)

- Dev. toxicity LOAEL 4 mg AgAc/kg bw/day / NOAEL 0.4 mg AgAc/kg bw/day (≡ 2.6 / 0.26 mg Ag+/kg bw/day).
  ∴ LOAEL lower than in 2-gen study with SZZ

- Mitigation: Effects moderate. 2^o effects area not well explored. MoA remains uncertain. Study not ideal vs TG 443 (EOGRTS)

Conclusion: As things stand likely to confirm RAC mindset re developmental tox of Ag^+

Ag^+ Fertility effects

Prior position

- No clear evidence for impact on reproductive performance at realistic doses. 2-gen studies on SCAS unremarkable

New

- Sprando study: Effect on fertility apparently detected (HD only; 26 mg Ag+/kg bw/day equivalent). Picked up in new SCAS CLH dossiers authored by Kemi as “severe”

- Mitigation: Effects not severe. Discordant with 2-gen evidence. Significant omissions in study design. 2^o effects?

Conclusion: Unwelcome, but mitigating science target areas are clear, e.g. if PMC EOGRTS can be progressed

Ag^+ Developmental immunotoxicity

Food and Chemical Toxicology 98 (2016) 195–200

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Food and Chemical Toxicology

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Effects of maternal silver acetate exposure on immune biomarkers in a rodent model

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ABSTRACT

Male and female rats (26-day old) were exposed to 0.0, 0.4, 4 or 40 mg/kg body weight silver acetate (AgAc) in drinking water for 10 weeks prior to and during mating. Sperm positive females remained within their dose groups and were exposed to AgAc during gestation and lactation. Splenic and thymic lymphocyte subsets from F1 generation PD (postnatal day) 4 and 26 pups were assessed by flow cytometry for changes in phenotypic markers. Spleens from PD4 pups had lower percentages of $CD8^+$ lymphocytes in 4 and 40 mg/kg AgAc exposed groups and reduced Concanavalin A (Con A) response at all AgAc exposure groups. Splenic maturation increased in PD26 pups compared to PD4 pups. Con A and lipopolysaccharide (LPS) mediated splenic responses were lower in PD26 pups exposed to 40 mg/kg AgAc. Changes in PD 26 pup splenocyte phenotypic markers included lower TCR + cells at 4 and 40 mg/kg AgAc exposure and higher B cell population in the 40 mg/kg AgAc. PD26 pup splenic natural killer cell (NK) activity was higher in the 0.4 AgAc group and unchanged in 4 and 40 mg/kg AgAc groups. In conclusion, maternal exposure to AgAc had a significant impact on rat splenic development during the early lactation period.

Published by Elsevier Ltd.

US FDA

- Same OGRTS on AgAc
- Published Dec 2016
- Immune parameters in offspring
- Long-term DIT work

Ag^+ Developmental immunotoxicity (DIT)

Prior position

- Clear concern triggers via Ag^+ adult immunotox lacking
  DIT studies poor / low relevance / evidence for DIT not robust

New

- Babu: Spleen lymphocyte populations affected in offspring
  Also some evidence for immune function effect of Ag^+

- NOAEL not demonstrated for 1x immune function parameter

- Mitigation: Not as powerful as EOGRTS DIT assessment.
  Uncertainty: actual dev. tox importance (refer to super-expert)

Conclusion: Impacts on: (a) extent of Ag^+ reprotox concern / classification; (b) DIT weight-of-evidence posn. in PMC TP

or maybe

Merits of a layered defence

Aim for defence-in-depth

Some optional spend now…aiming to save later

Even if Reprotox Cat. 2 argument is eventually lost, possess sufficient (effective) defensive science to prevent worst scenario of ionic Ag classification as Cat. 1B

Position of PMC EOGRTS Testing Proposal (TP)

Prior position

- TP pending with regulators/feedback still awaited
  Marginal data position on Ag^+ understood by WG
  Intersection with Ag NP toxicology also adds complexity

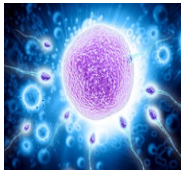
After Sprando/Babu

- If replicated, dev. tox & fertility effects would trigger extension EOGRTS (1B cohort; F_2 gen.). Also new DIT external trigger
- PMC TP now out of date ▶ **No option but to re-consider**
- PMC decision ▶ Science justifications for maintaining the TP
- Budget impact ▶ Complex EOGRTS should now be assumed

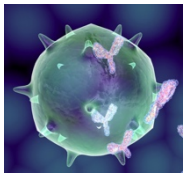
What could be done?

Key possibilities for PMC to consider re defensive actions

Ag^+ **Developmental Effects:** Mechanism of action: elaboration of MoA & relevance to humans. Attempt to differentiate if effects are primary reprotox or due to 2^o influences (mitigation value). Via targeted enabling studies before new EOGRTS?



Ag^+ **Antifertility Effect:** Evidence not yet strong. Flaws in Sprando et al. study methodology & completeness. Justify progression of new EOGRTS on this basis.



Developmental Immunotoxicity (DIT): Do better functional immunotoxicity evaluation – biological significance. Add DIT design into revised TP for EOGRTS (enabling work will be needed).

Why not study human reproductive effects of Ag?

Feasibility

- Epidemiology studies on chemical reproductive effects are feasible (e.g. Pb, pesticides)
- But uncertainties: multiple repro endpoints, detection sensitivity, discrimination power etc.
- Typically requires several large studies of exposed humans

Likely influence

- Infeasible in time available before CLH decision
- Also ECHA have tended to disregard such epi studies
- Example borates: classified Repro 1B even though available epi not supportive of conclusion of human reproductive effects

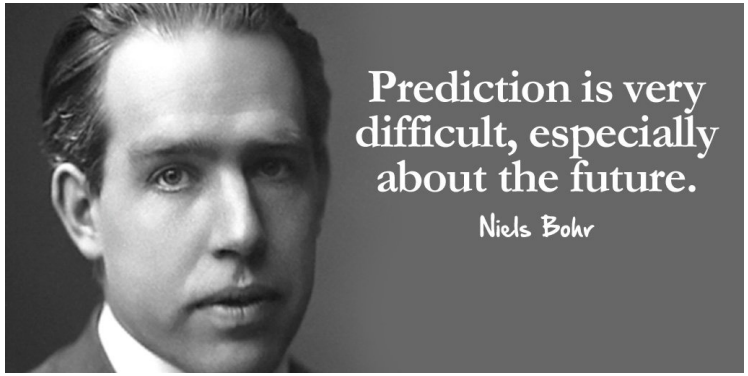
[Duydu et al. Is Boric Acid Toxic to Reproduction in Humans? Assessment of the Animal Reproductive Toxicity Data and Epidemiological Study Results. Curr Drug Deliv. 2016]

Chances of industry success

At least moderately good

But defence project requires commitment & energy

Work fast before decision precedents / other data overtake

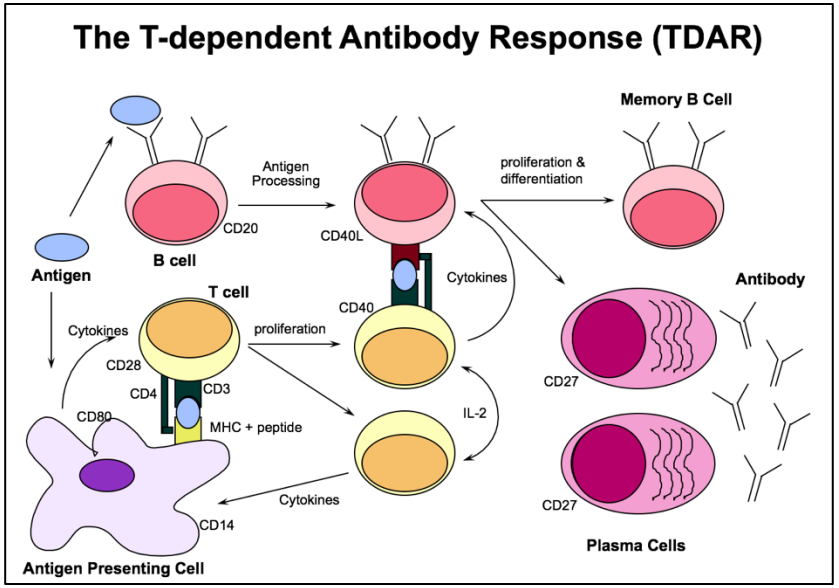


5.2 Need for revision testing proposal / study design ?

Holsapple review:

➢ Babu et al study:

- Provides **suggestive** evidence for possibility that Ag exposure can cause DIT → possible trigger for inclusion **DIT cohort** in our EOGRTS
- **Weaknesses**:
  - Lack of dose-response for **splenic** mitogenic responses
  - No Ag induced **thymic** effects (consistent with earlier studies)
  - Selected functional immunotox parameter not optimal in terms of predictive power → **TDAR** is gold standard (include in TP)
  - Lack of evidence for **adult** animal immunotox (e.g. van der Zande et al.) – very unusual to see DIT with no immunotox in adults (but Babu et al. did not examine P generation)



Need for revision testing proposal / study design ?

Holsapple review:

- van der Zande et al.: **distributional analysis** showed liver and spleen had highest levels of Ag (include in TP)
- Possibility of indirect effects (stress, gut microbiota impacts) in Babu et al. and Sprando et al. (reason for revision dosing in TP – exclude possibility of indirect effects)
- EOGRTS should generate the results that would enable proper assessment of DIT effects of Ag

Need for revision testing proposal / study design ?

Suggestions for TP:

- Inclusion **DIT cohort** (with assessment of TDAR)
- Inclusion **DNT cohort**?
- Inclusion **distributional analysis** in both P and F generations
- Revision **Ag doses** to be used, taking into account possible stress-induced responses

FOR DISCUSSION

5.3 Need for enabling studies before EOGRTS ?

- Enabling toxicokinetics investigations?
- How to exclude confounding indirect effects?

FOR DISCUSSION

Precious Metals Consortium

6. Workplan and budget

2017 expenses

2017 Budget to be spent	Expenses by 31/08/2017
897 550 €	376 211 €

- **SEv**: approx. 280 k€ less spent than budgeted:
  - Soil fate testing not needed
  - Ecotox testing and use update less than budgeted

2018 budget

	Total 2018 budget for Ag metal group	Ag metal (incl. Nano)	Ag remaining compounds
Total Budget	**1.041.706 €**	**512.603 €**	**529.103 €**
REACH PLATFORMS			
REACH dossier maintenance	***42.000 €***	**5.250 €**	**36.750 €**
Rolling maintenance	*42.000 €*	5.250 €	36.750 €
Literature review	*42.000 €*	*5.250 €*	*36.750 €*
REACH evaluation	***800.000 €***	**400.000 €**	**400.000 €**
Dossier evaluation	*800.000 €*	400.000 €	400.000 €
Extended one generation reproductive toxicity study (EOGRTS)	*800.000 €*	*400.000 €*	*400.000 €*
REACH classification & labelling	***15.000 €***	**15.000 €**	**- €**
Consultancy costs for providing comments on CLH proposals (+5% contingency)	*15.000 €*	*15.000 €*	*- €*
Internal and external fixed Scientific Managers	***184.706 €***	**92.353 €**	**92.353 €**
Building reserves	**- €**		
NON REACH PLATFORMS			
SVHC Roadmap			
Silver EQS			

2018 budget – changes since March WG meeting

- **SEv**: 2018 budget for 2nd tier (soil fate testing) removed since 1st tier was sufficient and dossier updated/submitted by July 2017 (contingency → budget available in reserves)
- **EOGRTS**: 2018 budget previously included 2 EOGRTS (bulk Ag + nanoAg) but unlikely that both studies will have to be conducted in parallel. Options:

1	TP accepted as submitted and testing only on bulk Ag	Need only budget for 1 EOGRTS
2	TP not accepted as such since ECHA wants to have nanoAg tested and extrapolate from nano to bulk to avoid animal testing	Need only budget for 1 EOGRTS
3	If outcome of nanoAg testing positive and if we can argue that additional EOGRTS is needed on bulk Ag	Need 2nd budget for EOGRTS but not before 2020 at the earliest

=> Mgmt Cttee recommended to remove budget for EOGRTS on nanoAg from 2018 budget

If WG wants to have budget for 2nd EOGRTS included again in 2018 budget: justification needed!

2018 budget – further changes?

- Add budget for **sediment testing**?
- Increase **EOGRTS** budget?
  - Enabling work
  - DIT, DNT cohorts, F2 generation

FOR DISCUSSION

Precious Metals Consortium

7. AOB, next meetings/calls and closing remarks

Amendments REACH Annexes to address nanoforms

- Open for feedback until 6 Nov
- PMC currently assessing impact on dossiers
- EM meeting 23 or 24 Oct

Next Ag WG meetings:

- **Thu 15 March 2018**
- **9, 10 or 11 Oct 2018**

THANK YOU

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