Precious Metals Consortium

Precious Metals & Rhenium Consortium

Silver Tox Experts Call PMC / ESTF

28 September 2018

Welcome and introduction

Confidentiality reminder

Terms of the non-disclosure agreement signed in December 2013 by PMC and ESTF apply.

Tour de table

Scope of REACH Ag Dossier and Ag Biocide Dossier

	Ag REACH	Ag BPR
Scope	**PMC** 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	RIVM, Dutch CA (SEv) ECHA (DEv)	KEMI, Swedish CA
CLH	Not a requirement (only as a possible conclusion from the SEv itself)	Requirement

Silver REACH dossier covers 3 forms:

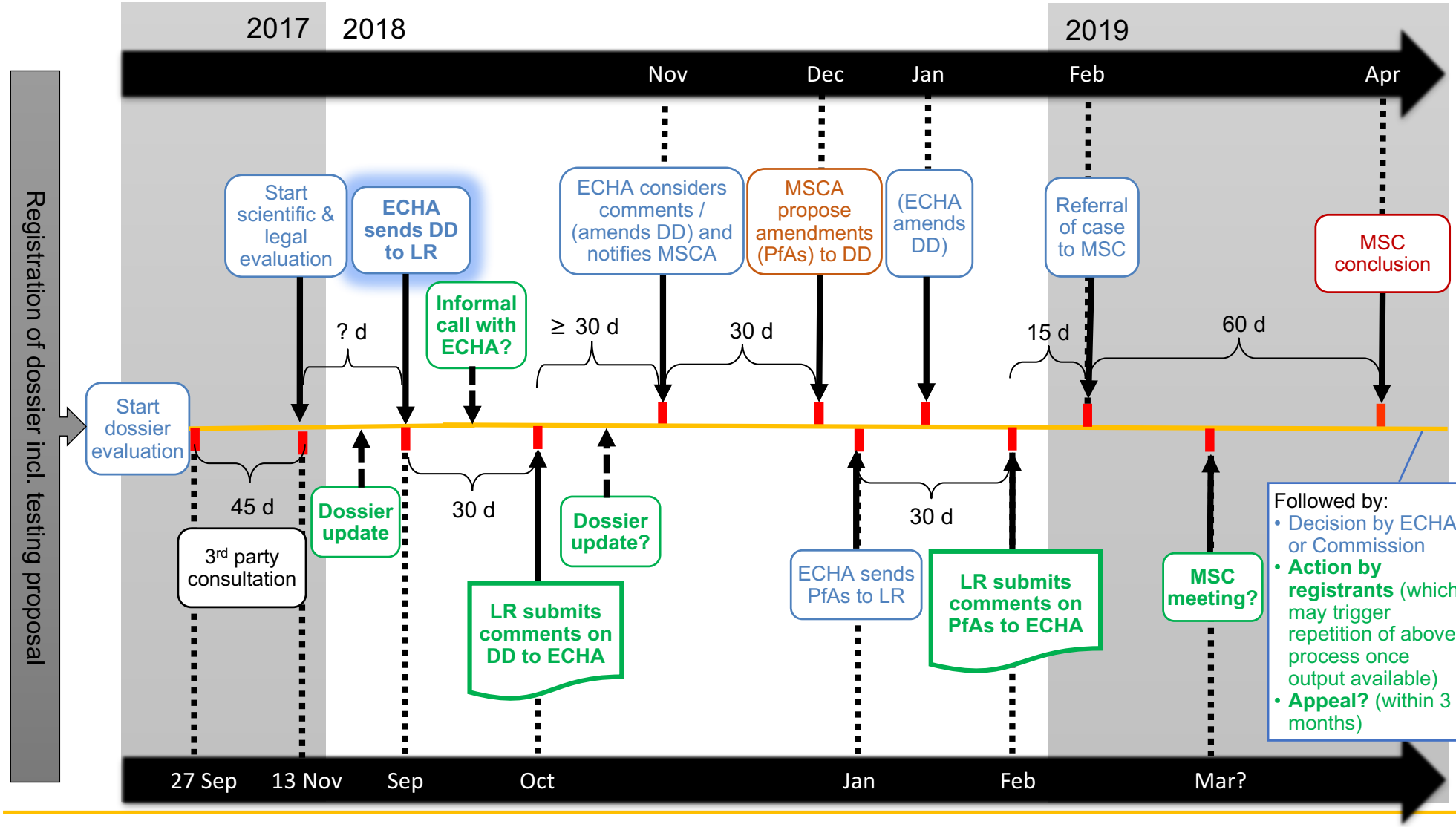
- Massive (> 1 mm)
- Powder (100 nm – 1 mm)
- Nano (< 100 nm)

Current situation silver reprotox

- Ongoing discussions under BPR on **classification of SCAS**
  - SZZ: Repr cat. 1B proposed, cat. 2 agreed; RAC mainly attribute effects to Ag^+
  - SZ and SCZ: Repr cat. 2 proposed
- **Data gap** on reprotox → PMC submitted original **TP for EOGRTS** in 2015 (AgAc)
- Since 2015: further research published suggesting Ag is reprotox
  - maybe even **Repr cat. 1B?**
  - several weaknesses in recent silver research → data gap still remains, but **update of TP** was necessary
- **TP updated** April 2018:
  - Addition of recent studies to the TP / registration dossier
  - Addition of developmental immunotoxicity (DIT) cohort to the EOGRTS design
  - Need for enabling studies on the mode of action (MoA) prior to the EOGRTS final dose-setting and study start
  - Revision of dose-setting
- Even if TP accepted: outcome of EOGRTS is highly unpredictable and **risk of classification as Repr cat. 1B** still exists
- Outcome EOGRTS **relevant for PMC and ESTF**

Status EOGRTS TP

DD = Draft Decision
LR = Lead Registrant
PfAs = Proposal for Amendments



Meeting PMC and ESTF 5 July 2018 and follow-up

- Agreement between ESTF and PMC to further **share communication KemI / ECHA** and to potentially **align efforts / advocacy actions** related to Repr classification after internal discussion

- **$AgNO_3$**
  - considered corrosive → read-across from other SCAS
  - ESTF 28d gavage RDT study with $AgNO_3$ (2016) not accepted by KemI as incorporating MTD (@ 100 mg/kg bw/d) → need to fill data gaps for CMR → options are test and/or read-across (e.g. to AgAc reprotox)
  - KemI intends to prepare **CLH proposals for $AgNO_3$ and Ag** incl. **Repr 1B** classification based on data AgAc, AgCl and SZZ → implications for other Ag compounds / SCAS
  - KemI: "*[ESTF] welcome to submit a revised version of the position paper to strengthen the read across approach. We will of course take it into consideration for the CLH dossiers.*"

- EPMF would prefer that EOGRTS can proceed before CLH decision is made by RAC → request for joint meeting EPMF / ESTF / ECHA / KemI

- **Read-across** approach ESTF questioned by KemI, EPMF also looking into possibilities to strengthen their read-across approach

EPMF Read-across approach

- Based on 3 parameters which are expected to drive bioavailability and tox:
  1) **Water solubility**
  2) **Valency**: Ag(1+) considered to be the relevant species under physiological conditions which potentially exerts the tox effect
  3) **Bioaccessibility**

- Bioaccessibility data from Midander and Wallinder (2009)

Table IV. Total concentration of released silver [µg/L] in the different test media

Test Material	GST	ALF	ASW	GMB	PBS
	Ag conc. µg/L	Ag conc. µg/L	Ag conc. µg/L	Ag conc. µg/L	Ag conc. µg/L
Ag-1 2h	36.7±6.8	131.3±1.2	215.0±1.0	282.7±6.7	349.0±7.5
Ag-1 24h	35.3±1.2	123.0±1.0	224.0±59.8	270.0±3.5	352.3±6.5
Ag_2O 2h	36.0±1.0	129.3±1.2	190.0±7.8	237.3±41.3	281.7±6.4
Ag_2O 24h	36.0±1.0	123.0±0.0	184.7±2.1	264.3±1.5	338.0±2.6
Ag-2 2h	42.0±2.6	127.7±1.2	209.3±14.6	278.3±8.1	280.7±92.2
Ag-2 24h	42.0±1.0	120.3±0.6	184.0±1.0	260.3±1.5	340.0±1.0
$AgNO_3$ 2h	36.0±1.0	127.0±1.0	190.0±1.0	272.0±5.2	355.7±11.6
$AgNO_3$ 24h	34.0±1.0	120.0±1.0	186.0±2.6	259.3±1.5	347.3±2.1

  - Cl conc. in media drove absolute equilibrium concentration of dissolved Ag (independent of tested Ag substance)
  - Dissolved Ag always <0.5% irrespective of substance; this does not match *in vivo* oral bioavailability data
  - Early dissolution kinetics (stable by 2h)

ESTF Read-across approach

- **Ag^+** is the common species released from all SCAS, and is responsible for the biocidal activity
- Read-across (tox effects) based on measured silver release under comparable experimental conditions.
- Availability = Ag^+ release (%) x silver content (%) of material
- Tox effects read across from high availability to low or similar availability, but not vice versa
- Release data from O'Connor and Woolley (2010)

SCAS name	Reaction mass of SiO_2 and silver (nano)	Silver zinc zeolite	Reaction mass of TiO_2 and silver chloride	Silver phosphate glass	Silver phosphate glass	Silver copper zeolite	Silver zinc zeolite	Elemental silver	Silver sodium hydrogen zirconium phosphate	Silver nitrate
Abbreviation	Ag/SiO_2	SZZ B502i	$TiO_2/AgCl$	Ag glass IPL	Ag glass IPM	SCZ	SZZ AK	Ag	$AgZrPO_4$	$AgNO_3$
Silver content	20%	2.1%	15.1%	1.9%	2.4%	3.5%	4.9%	100%	9.9%	64%
24 hour PBS pH4, 37°C	8.6 mg/L[a]	19 mg/L	3.3 mg/L	28 mg/L	27 mg/L	18 mg/L	18 mg/L	1.1 mg/L	14 mg/L	Fully soluble
	0.6%	37%	6.5%	56%	53%	37%	37%	2.2%	27%	100%
Availability	**0.001**	**0.008**	**0.010**	**0.011**	**0.013**	**0.013**	**0.018**	**0.022**	**0.027**	**0.64**

Complex picture on bioavailability of Ag

- Both EPMF & ESTF read-across approach flawed:
  - **EPMF** bioaccessibility testing: complex equilibria involving AgCl, but also Ag complexes of varying solubility and toxicity. Plus S/Se sequestration *in vivo* etc.
  - **ESTF** release testing: PBS systems not proper surrogates for stomach & intestine + lower pH for GST
- ESTF model used to read-across / gap fill: tox data gap for higher BA simple Ag salts (nitrate, chloride); elemental Ag SCAS → see next slide

Relationships if ESTF 'bioavailability' (BA) / read-across model is applied to Reprotox

	SZZ	Ag (elemental)	SSZHP	(AgAc) Not a SCAS	$AgNO_3$
Rank Ag^+ BA value (scaled ex. ESTF bioelution testing program)	**0.018**	**0.022**	**0.027**	**(0.1)** See footnote	**0.64**
Key reprotox datapoint (2-gen / OGRTS):	**Clear embryo-fetal effects in 2-gen study.** Rep Cat. 2	**Not yet assessed.** Read-across proposed !	**Only limited embryo-fetal effects in 2-gen study.** Not classified	**Clear embryo-fetal toxicity (OGRTS).** Fertility effect HD. DIT also reported.	**Not yet assessed.** Read-across proposed !

Notes:

SZZ = Silver Zinc Zeolite Ag elemental is a massive form SSZHP = Silver Sodium Hydrogen Zirconium Phosphate

ESTF bioelution results are from a simple PBS system at pH 4 or 10 (no lower pH data is incorporated).

AgAc not in program / bioelution untested in ESTF model; crude extrapolation here is based on comparative solubility to $AgNO_3$.

Due consideration given to equivalent Ag^+ dose & comparative LOAEL/NOAEL in interpretation of reprotox studies. Note that greater general systemic toxicity was also evident in the SZZ testing (based on normalised Ag^+ equivalent doses).

Possibilities for further bioavailability modelling / testing

Tier 1	**Data-mine existing TK**: • Literature data mainly on nanoAg but also $AgNO_3$, AgAc • TK data ESTF (from RDT studies)?
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 (Henderson et al. 2012, Denys et al. 2012, Colombo et al. 2008, Turner et al. 2008) • Importance of identifying exactly which Ag substances need to be tested (Ag content can vary for some of the SCAS; important to identify which SCAS were used in the different reprotox / RDT studies) • Preliminary cost estimate for combined 'gastric / post-gastric' bioelution (depending on used media / materials): 8-10 k€ for first test item, 6.5-8 k€ for additional test items
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

FOR DISCUSSION

How to achieve regulatory acceptance of further studies

- It would not be sensible for industry to develop a BA programme to further justify read-across without buy-in from stakeholder agencies (ECHA & KemI)
- Opportunities:
  1. Through the MISA framework:
     - MISA workshop 2 Oct on HH read-across (Eurométaux and ECHA)
     - Follow-up actions related to this workshop, where EPMF will have an opportunity to interact directly with ECHA on the Ag case (e.g. blog, detailed workplan per metal/metal group).
  2. Through DEv process and EPMF's comments to the DD / interactions with ECHA.
- Importance of focusing on science argumentation → better **TK data** needed before comparative bioavailability can be read-across properly
- Joint meeting **ESTF / EPMF / ECHA / KemI**

FOR DISCUSSION

Next steps

- Strategy doc to be further updated
- F2F meeting to further discuss testing strategy?

THANK YOU

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