

Precious Metals and Rhenium Consortium Ag WG meeting

Hotel Montgomery - Imperial Room
Avenue de Tervuren 134 – 1150 Brussels
27 March 2013
10:30 – 15:00 CET



1. Introduction and welcome

- Competition Law reminder
- Approval of the Agenda
- Approval of minutes last meeting



Nano-silver update



Nano Ag TF Update

- Work progressing as planned
  - Lit. review completed (see next slides WCA)
  - Agreed read across from ionic Ag+ to nano-silver
    - Confirmed at 3 Dec. 2012 Ag WG mtg
- Ongoing work
  - ASRIT test (OECD 209) at LAUS, Germany
  - Waiting for key data (CSIRO soil data, NTP feeding studies)
- For discussion with Ag WG
  - Classification of nano-Ag – *agenda point 3*
  - PNEC marine update – *agenda point 2*

Registration strategy

- No explicit guidance on which data requirements apply to the nano form of a substances
  - » usually comprise only a small portion of overall tonnage
- Registrant must ensure the safety of **all forms** included in the registration
  - » provide adequate information to address the relative hazard/properties of the different forms, including CSR
- This can be based on read-across
  - » Must be scientifically justifiable
    - o *Sufficient evidence to read-across to nano silver from ionic silver?*

Registration strategy – administrative aspects

- Updated guidance clearly indicates that ECHA expect a single dossier to be submitted that covers the hazard and risk assessment of both forms
- Possible that data could be presented as two separate CSR attached to the IUCLID file
- However, since read across to ionic silver provides a precautionary assessment of the environmental toxicity and fate of nano silver, presenting a single CSR would be the simplest and most effective way to report this data, at least for the environmental sections
- Our recommendation would therefore be that a single CSR, containing all the hazard data for ionic and nano silver and the justifications for this, is produced and attached to the dossier

Summary of registration strategy recommendations

- Single REACH registration prepared
  - » **All** forms of silver marketed in the EU
- Some additional testing is recommended to reduce uncertainty associated with the read across for some endpoints:
  - » OECD 209 test (Activated sludge respiration test) – potentially with modifications to assess impact on nitrification.
- The impact of a revision to the marine PNEC should be assessed
- Watching brief on the availability of additional terrestrial effects and sediment data for nano silver (plants and microorganisms)

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2. PNEC marine water



Marine PNEC

- Nano literature search identified new study on nano Ag with Oysters: very low PNEC
- Data is relevant and reliable - need to take into account – cannot dismiss
- NOEC < PNEC = current PNEC not protective
- Effects likely related to ionic silver, not to nano Ag
- Further discussion + options for addressing this: next slides WCA

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Options appraisal for revision of the marine PNEC for silver under REACH

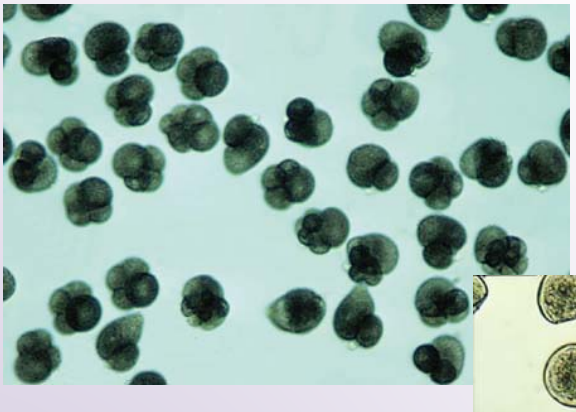
Peter Simpson

Employee Ownership Association
ISO 9001 REGISTERED FIRM
ISO 14001 REGISTERED FIRM

Background

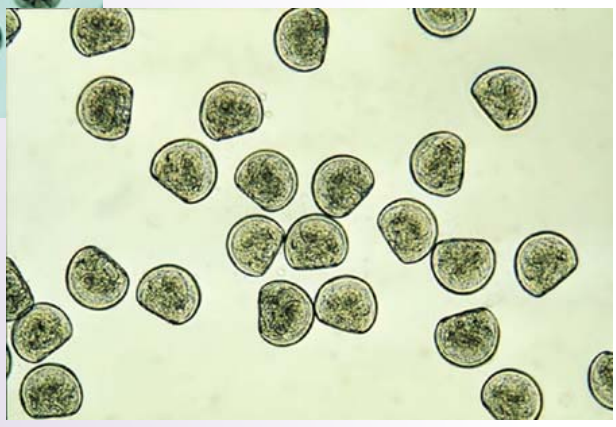
- Existing $PNEC_{marine}$ for silver is 0.86 µg l^{-1}
  - » Derived using full salinity data (30-35 ppt), but also accommodated data from lower salinities
  - » As salinity reduces toxicity is known to increase
  - » $PNEC_{marine}$ should include all salinity ranges beyond tidal limit
- New data - Ringwood et al. (2010)
  - » American oyster - *Crassostrea virginica*
  - » 25 nm silver nanoparticles – no coating
  - » 25 ppt salinity / 25 °C / 48 h exposure / embryonic development
  - » NOEC: 0.16 µg l^{-1} / LOEC: 1.6 µg l^{-1}
  - » Cannot conclude a nano-specific effect
  - » Could be a very sensitive result associated with ionic silver
    - o *No reference testing reported*
  - » Not an ideal study, but sufficiently reliable as supporting data

Oyster embryo larval development testing



- Short exposure duration (24 – 48 hours)
- Development from embryos to 'D' shaped larvae

Very sensitive life-stage



Consequences for silver dossier?

- NOEC below existing $PNEC_{marine}$
  - » difficult to robustly accommodate "qualitatively"
- Is this evidence for a nano-specific effect?
- Result is not compatible with read-across strategy
  - » For other endpoints ionic silver is **always more toxic** that nanosilver based on evidence in scientific literature
    - o *Confirmatory testing underway for microorganisms where weight of evidence was equivocal*
- Does this affect read-across for powders as well as nano?
- Will a revision to the $PNEC_{marine}$ or nano-specific $PNEC_{marine}$ be required?

Regulatory context

- $PNEC_{marine}$ in silver dossier based on Environment Agency (UK) EQS report for silver as a potential WFD specific-pollutant
  - » Not adopted as a SP as lack of evidence of exposure
- RIVM (NL) environmental risk limits for silver in the marine environment: 0.012 to 0.090 µg l^{-1}
  - » Based on speciation modelling, not supported by empirical evidence
  - » PMC consider the RIVM risk limits to be very precautionary
- Silver subject to Evaluation under REACH
  - » led by NL

Aims and objectives

1. Outline the range of options available to address issues identified
2. Explore the potential implications of a revision to the $PNEC_{marine}$
   - » Perspective of risk characterisation for CSR and ES
3. Propose option/s for addressing the new data

Candidate revised $PNEC_{marine}$

- Different PNEC can be derived based on selection of either different critical data or different assessment factors
- All valid - but have different assumptions regarding the importance of relationship between salinity and toxicity

PNEC option scenario	(µg L^{-1})	Derivation basis	Reference
S1	0.860	critical data of 8.6 µg L^{-1} / AF of 10 - *current* $PNEC_{marine}$	Ward et al. (2006)
S2	0.172	critical data of 8.6 µg L^{-1} / AF of 50	Ward et al. (2006)
S3	0.100	critical data of 5.0 µg L^{-1} / AF of 50	Nelson et al. (1983)
S4	0.040	f/w SSD HC_5 / AF of 3 - *current* $PNEC_{freshwater}$	-
S5	0.016	Based on critical data of 0.16 µg L^{-1} / AF of 10	Ringwood et al. (2010)

AF: Assessment factor

Risk Characterisation Sensitivity Analysis

Dataset	Total N° sites/uses	Number of sites/uses with RCR > 1				
		S1 (0.860)	S2 (0.172)	S3 (0.100)	S4 (0.040)	S5 (0.016)
Tier III Manufacturer[1]	39	0	0	0	0	7
Tier III Downstream user	9	0	0	0	0	0
ES – silver	14	0	0	0	0	1
ES – silver nitrate	12	0	0	0	0	2
ES – disilver oxide	6	0	0	0	0	1

1: Initial single manufacturer with RCR > 1. Tier III modelling refined to incorporate municipal STW step resulted in RCR of 0.3 and 0.8 for S3 and S4, respectively

Existing oyster embryo data for silver

Species	48-h EC50 (µg L^{-1} Ag)	Life-stage	Temperature	Salinity	Reference
C.virginica	5.8	1-h post fertilisation	26	25	Calabrese et al. 1973
C.virginica	24.4	1-h post fertilisation	20	33	MacInnes & Calabrese 1977
C.virginica	35.3	1-h post fertilisation	25	26	MacInnes & Calabrese 1977
C.virginica	32.2	1-h post fertilisation	30	26	MacInnes & Calabrese 1977
C. gigas	16 - 18	fertilised eggs	20	33	Coglianese & Martin 1981
C. gigas	22	fertilised eggs	20	33	Martin et al 1981
C. gigas	13	fertilised eggs	20	25	Coglianese 1982
C. gigas	9	fertilised eggs	20	20	Coglianese 1982
Mercenaria mercenaria	21	1-h post fertilisation	26	25	Calabrese & Martin 1974
Mytilus edulis	14	fertilised eggs	17	33	Martin et al 1981
Spisula solidissima	14	1-h post fertilisation	20	32 - 33	Zoto & Robinson 1985
C.virginica	0.49	fertilised eggs	25	25	Ringwood et al. 2010

Existing oyster embryo data for silver

- EC50 values range from 5.8 to 35.3 µg L^{-1}
- Studies from 1970s and 1980s
  - » Methodology not significantly changed in this period
- An order of magnitude less sensitive than Ringwood et al. (2010) study
- PNEC would be based on EC10/NOEC rather than EC50, but slope of dose-response in oyster tests is usually steep

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Conclusions

- Ringwood data is not compatible with the read-across strategy for silver
- Various revisions to the $PNEC_{marine}$ can be proposed based on either different critical data or different Assessment Factors
- Two $PNEC_{marine}$ scenarios did not result in RCR values >1 but were low enough to accommodate Ringwood data and re-establish robust-read across
  - » S3: 0.100 µg L^{-1} / S4: 0.040 µg L^{-1} – f/w PNEC
- Also reflect estuarine as well as marine conditions
- Context: Both similar to RIVM thresholds

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Options

1. Do nothing
2. $PNEC_{marine}$ for silver is revised to 0.100 µg L^{-1}
3. $PNEC_{esturaine}$ for silver is established at 0.100 µg L^{-1}
   - » Exposure scenarios for silver and silver substances are revised to account for this revision
4. Undertaken additional comparative testing (with appropriate particle controls) to confirm the sensitive result reported by Ringwood et al (2010)

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Do nothing

- **Strengths**
  - » No revision to dossier – low admin
- **Weaknesses**
  - » No response to new data
- **Opportunities**
  - » Undertake additional testing to confirm findings of new data
- **Threats**
  - » $PNEC_{marine}$ could be a focus during evaluation process

Revise $PNEC_{marine}$ to 0.100 µg L^{-1}

- **Strengths**
  - » Relatively simple revision
  - » Accommodates new data
  - » No change to Exposure Scenarios required to demonstrate safe use
  - » Immediately restores read-across
  - » $PNEC_{marine}$ more explicitly relevant to esturaine/transitional conditions where toxicity is known to be higher
- **Weaknesses**
  - » Reduces $PNEC_{marine}$ significantly
- **Opportunities**
  - » May be more acceptable to NL during Evaluation
  - » Additional time to conduct confirmatory testing
- **Threats**
  - » Reduction in margin of safety in exposure scenario RCR which may be important in the future

Establish $PNEC_{estuarine}$ or 0.100 µg L^{-1}

- Strengths
  - » Accommodates new data
  - » No change in exposure scenarios required to demonstrate safe use
  - » Immediately restores read-across
  - » Explicitly relevant to estuarine/transitional conditions where silver toxicity is known to be higher
- Weaknesses
  - » Introduces an additional layer of complexity to exposure assessment
- Opportunities
  - » Additional time to conduct confirmatory testing
- Threats
  - » Reduction in margin of safety in exposure scenario RCR which may be important in the future
  - » May not be welcomed by NL during evaluation

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Undertake additional testing

- Strengths
  - » Addresses uncertainty in Ringwood data
  - » New data would be backed by quality system / analytical chemistry and GLP
  - » Any response based on results of confirmatory testing would be supported by evidence, rather than a lack of evidence
- Weaknesses
  - » Does not address new data immediately
  - » Could be relatively expensive
- Opportunities
  - » Potential to dismiss Ringwood study as unreliable
- Threats
  - » Potential that sensitivity of Ringwood study could be repeated in GLP study, which would have to be used for PNEC derivation, rather than as supporting data
  - » May still become the most sensitive marine data, even if not as sensitive as Ringwood – prompting a review of the $PNEC_{marine}$

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3. Classification of Ag metal – Final Discussion



Three Ag grades

	Particle size	Classification	Comment
Massive Ag	> 1 mm	Not classified	Confirmed by new TD test, cf. agenda point 4.1
Powder Ag	< 1 mm	Acute 1/ Chronic 1	Based on TD test
Nano Ag	< 0.0001 mm	Acute 1/ Chronic 1	Based on read across from Ag^+

- Dec. 2012 General Assembly Mtg.
  - Decision to cover all 3 forms in 1 Ag dossier = add nano Ag
  - BUT
    - Must have no negative impact on other Ag grades
    - Must be conform with CLP guidance



Guidance on the Application of CLP Criteria

Version 3.0 – Nov. 2012, Annex IV.5.5 (emphasis added)

" Normally, the classification data generated would have used the smallest particle size marketed to determine the extent of transformation. There may be cases where data generated for a particular metal powder are not considered as suitable for classification of the massive forms. For example, where it can be shown that the tested powder is structurally a different material (e.g. different crystallographic structure) and/or it has been produced by a special process and is not generally generated from the massive metal, classification of the massive can be based on testing of a more representative particle size or surface area, if such data are available. The powder may be classified separately based on the data generated on the powder. However, in normal circumstances it is not anticipated that more than two classification proposals would be made for the same metal.

Metals with a particle size smaller than the default diameter value of 1 mm can be tested on a case-by-case basis. One example of this is where metal powders are produced by a different production technique or where the powders give rise to a higher dissolution (or reaction) rate than the massive form leading to a more stringent classification. "



Classification - CLP Guidance

- Discussion
  - Guidance more targeted at massive vs. powder metals
  - Purpose of classification: most appropriate classification based on intrinsic properties => if different forms have differing properties this should be reflected in the classification
  - Does not exclude > 2 classifications
  - Nanomaterials not specifically considered in guidance. Could be considered beyond 'normal circumstances'



Classification of Ag metal - Agreed

	Particle size	Classification	M factors	Rationale
Massive Ag	> 1 mm	Not classified	None	Confirmed by new TD test, cf. agenda point 5
Powder Ag	< 1 mm	Acute 1/ Chronic 1	1/10	Based on TD test
Nano Ag	< 0.0001 mm	Acute 1/ Chronic 1	1000/ 100	Based on read across from Ag^+

- NL Evaluation will focus on substance form/characterisation
- Need to provide robust rationale that massive ≠powder ≠nano
- More stringent M-factor for nano Ag should be acceptable to NL



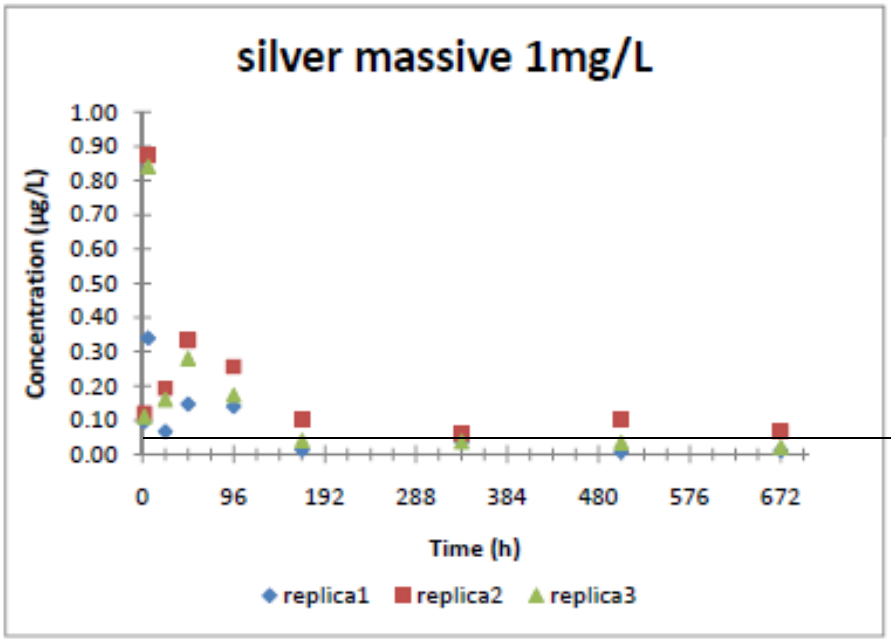
4. Updates



4.1 TD-Tests Massive Silver



Massive Ag – Initial TD test 2010



PNEC:
0.04 ug/l !



Massive Ag – Initial TD test 2010

1mg/L		Ag (µg/L)									
		0	2	6	24	48	96	168	336	504	672
Reporting Limit		0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
replica1	spl1		0.05	0.25	0.04	0.10	0.13	0.00	0.01	0.00	0.01
	spl2		0.11	0.32	0.06	0.15	0.14	0.01	0.09	0.01	0.01
	spl3		0.14	0.45	0.10	0.19	0.15	0.03	0.01	0.01	0.01
	average		0.10	0.34	0.07	0.15	0.14	0.01	0.04	0.01	0.01
	stdev		0.05	0.10	0.03	0.05	0.01	0.02	0.05	0.01	0.00
	CV (%)		48	30	46	31	7	115	126	87	-
replica2	spl1		0.12	0.53	0.19	0.37	0.25	0.10	0.09	0.10	0.06
	spl2		0.14	0.81	0.20	0.29	0.27	0.11	0.08	0.10	0.07
	spl3		0.11	1.28	0.19	0.34	0.25	0.10	0.01	0.11	0.07
	average		0.12	0.87	0.19	0.33	0.26	0.10	0.06	0.10	0.07
	stdev		0.02	0.38	0.01	0.04	0.01	0.01	0.04	0.01	0.01
	CV (%)		13	43	3	12	4	6	73	6	9
replica3	spl1		0.11	1.34	0.15	0.26	0.17	0.04	0.03	0.04	0.02
	spl2		0.14	0.95	0.18	0.29	0.17	0.04	0.04	0.03	0.02
	spl3		0.09	0.23	0.15	0.29	0.18	0.04	0.04	0.03	0.02
	average		0.11	0.84	0.16	0.28	0.17	0.04	0.04	0.03	0.02
	stdev		0.03	0.56	0.02	0.02	0.01	0.00	0.01	0.01	0.00
	CV (%)		23	67	11	6	3	-	16	17	-
	average		0.11	0.68	0.14	0.25	0.19	0.05	0.04	0.05	0.03
	stdev		0.01	0.30	0.07	0.10	0.06	0.05	0.01	0.05	0.03
	CV (%)		11	44	47	38	32	89	30	104	94
Pooled	stdev		0.03	0.40	0.02	0.04	0.01	0.01	0.04	0.01	0.00
Pooled	CV (%)		29	58	15	14	5	18	83	12	10

coloured if >10%
coloured if >10%
coloured if >10%
coloured if >20%
coloured if >20%

- **28d value < PNEC**
- **But all other values > PNEC**
- **Repeat TD test necessary**



Massive Ag – TD repeat 2012/3 (draft results)

- Draft results – report by early March

		silver	3mg/L loading (surface equivalent)								
time (h)		0	2	6	24	48	96	168	336	504	672
Reporting Limit		0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
replica1	spl1		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	spl2		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	spl3		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	X		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	σ		-	-	-	-	-	-	-	-	-
	CV (%)		-	-	-	-	-	-	-	-	-
replica2	spl1		<0.02	<0.02	0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	spl2		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	spl3		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	X		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	σ		-	-	-	-	-	-	-	-	-
	CV (%)		-	-	-	-	-	-	-	-	-
replica3	spl1		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	0.04
	spl2		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	spl3		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	X		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	σ		-	-	-	-	-	-	-	-	-
	CV (%)		-	-	-	-	-	-	-	-	-
	X		<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
	σ		-	-	-	-	-	-	-	-	-
	CV (%)		-	-	-	-	-	-	-	-	-





Massive Ag – TD testing

- Classification massive Ag
  - Chronic class. Is based on 1mg/l loading rate, 672h (28d)
  - Tested 3 loading rates: 3, 9, 27 mg/l (surface eq.)
  - Need to extrapolate to 1 mg/l
- Need to explain why new data is more relevant than initial data
  - Artifacts in initial test due to possible contamination of resin surface with Ag powder
  - Better cleaning of glass surface in second test (ultrasonication) - glass vs. resin surface
  - Minimized absorption in second test = worst case, should have resulted in even higher levels





4.2 Preparation for Evaluation



Evaluation

- Background
  - CoRAP list 20 March 2013: Ag selected for Evaluation in 2014
  - Duration: 1 yr.
  - Rapporteur member state: The NL (RIVM)
  - 'Initial grounds for concern': *Nanoparticles/ Toxicity of different forms of the substance; Exposure/Wide dispersive use; Consumer use; Aggregated tonnage*
  - Thorough review of dossier: explicitly not limited to "initial grounds for concern" = whole dossier will be reviewed



Evaluation

What happened previously

- Silver initially listed for Evaluation in 2013
  - Strategy for Evaluation agreed at General Assembly June 2012
- Contacted RIVM Evaluation unit
  - Contacted on 13 April 2012 and 30 May 2012
  - NL responded 8 June 2012: not ready yet, suggest exchange in Q3/4 2012
  - Oct. 2012: official confirmation that Evaluation postponed (due to workload issues at NL level)
  - Other contacts with RIVM (s. next slide)



Evaluation

- Interactions RIVM
  - RIVM publishes report 'Env. risk limits for Ag in water' in 2012
    - Proposes overly conservative limit values for Ag: 10 ng/l Ag freshwater, 10-90 ug/l Ag in marine waters
    - Further discussion: agenda point 4.3
  - Testing Proposals Soil
    - NL comment (22nd Feb. 2013): (emphasis added)

"The Netherlands agrees to the DD provided that what is covered by the analogue substance, silver nitrate, is the non-nanomaterial form of silver only. In order to avoid confusion, this should be clearly indicated in the DD. It is noted that the registered substance is identified under the CAS registry number 7440-22-4. This identifier covers all forms (bulk form and nano-form) of silver. In view of reported (potential) differences between nano and bulk silver, it is important that it is clearly stated whether this TPE covers the bulk form only and/or if it is supposed to cover bulk and nanomaterial. In the latter case a proper scientific substantiation should be provided.
In the DD ECHA considers the proposed read-across and grouping approach as plausible and the Netherlands supports this view. The registrant is reminded that for a proper read-across the registered substance, as well as the read-across substance need to be properly characterized. Thus, in this case, both the registered substance silver (CAS No 7440-22-4) and silver nitrate (CAS No 7761-88-8)."

- PMC response agreed via 'written procedure', submitted 22nd March 2013



Evaluation

- Detailed Justification for selection on CoRAP (emphasis added)

"Silver is a widely used material for which 49 registrations are received. All registrations for silver are submitted under CAS-nr 7440-22-4. It is necessary to extract and evaluate the substance characterization, (eco)toxicity, exposure and use information, if available, from each original study preferably divided over the different lines of production."

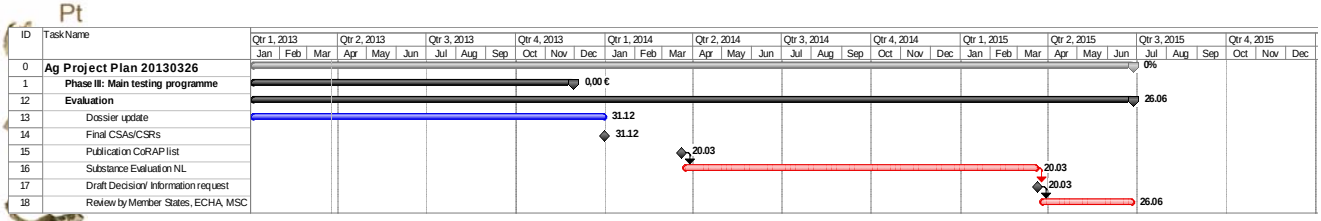
"A clear indication of the type/form of silver (size, size distribution, agglomeration state, coating etc) that is tested in each toxicity test to enable a proper evaluation of the risk of each form."

"If differences in hazard and exposure of the different forms are sufficiently large it may be anticipated that separate registrations are necessary for the different forms."

- Are NL targeting separate dossier for nano Ag?

Evaluation

- Next Steps/ Recommendation
  - Our read-across strategy is robust and defensible
  - Stick to agreed strategy, but ensure dossier explains read across in detail
  - Contact RIVM again to request initial meeting (draft letter circulated 26th March 2013)
  - Time line:



- Discussion

4.3 Other Updates



RIVM report 'Env. risk limits for Ag in water'

- Background
  - Suggests threshold value of 10 ng/l
  - PMC comments 17 Oct. 2012
    - Value overly conservative
    - Artificially low due to data selection (based on flawed study)
    - Does not consider all data
    - Does not follow correct methodology
    - UK Env. Agency derived EQS of 40 ng/l (used as PNEC in our dossier)
- RIVM response 01 Feb. 2013
  - *'It is decided not to reconsider the RIVM-report at this stage'*
- Next Steps
  - Put on hold?
  - Escalate to higher level?
  - Publish response in scientific journal, e.g., SETAC?
  - Other?



CSIRO – Scope

- Status
  - Project on schedule
  - Significant data generated already
    - Leached/unleached (unaged) soils have been tested
    - Additional tests on lability of Ag, speciation
    - Speciation
    - Presented initial data at SETAC NA mtg, Nov. 2012
  - Cf. detailed update, email 4th Feb. 2013
- Next Steps/Timing
  - Interim report April 2013
  - Complete testing
  - Draft final report Nov. 2013

CSIRO – Scope/ Time line

Task	2012									2013									
	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct
Microbial N transformation																			
conduct testing																			
soil digests																			
data analysis																			
Root elongation																			
conduct testing																			
soil solutions																			
soil digests																			
data analysis																			
Plant emergence & growth																			
conduct testing																			
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data analysis																			
Aging Experiment																			
spike/leaching aging soils																			
Ag lability determination																			
spike/leach non-aging soils																			
conduct toxicity testing																			
soil digests																			
plant digests																			
data analysis																			
Milestone reports																			
Soil properties																			
Ag lability/prelim plant & microbial toxicity																			
Ag toxicity to soil microorganisms																			
Ag toxicity and accumulation in plants																			
Ag toxicity to earthworms/aging results																			

Ag

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5. AOB



Thank you