Update of Ag dossiers submitted in 2010

(for PMC Members' information)

Background & Aim

In the three Ag dossiers submitted in 2010 testing proposals were included for soil toxicity and repeated dose (oral) toxicity. Following evaluation by ECHA, it appeared that:

- The soil toxicity testing proposal was considered redundant by ECHA as work had already been started (via a PMC Member based in the US)
- Before the 90d oral toxicity testing proposal could be evaluated, information from external data holders required consideration, the test item needed to be named together with read-across arguments, and the route of administration needed to be justified more precisely, specifically in the case of silver (relevance of inhalation vs oral exposure)

On 12 Dec 2011 the above bullet points were discussed with ECHA and industry committed to update the related dossiers by the end of February 2012.

Although according to Article 4.1.6.2 of the PMC Agreement PMC Members must be given 28 calendar days to respond to written proposals or requests for decision, considering the work to be done and the time pressure imposed in this case, this was not be feasible and the PMC Management Committee agreed to derogate from the rule and to reduce the time for response on the conditions that:

- The concerned co-registrants would be kept informed, as regularly as possible, on the underlying principles and general content of the updates in preparation
- Co-registrants would be given at least one week to respond on the final outline/summary of the update which will be circulated prior to mid-Feb 2012

The aim of this document is hence to inform PMC Members on the changes that will be made to the content of the Ag dossiers submitted in 2010 as result of ECHA's draft decisions on the testing proposals included in the dossiers and the further exchanges which took place between ECHA representatives, Lead Registrants, PMC Chairpersons, Secretariat and expert consultants since Nov 2011.

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Adjustments to the Ag Dossiers

Following many exchanges with WCA, CSIRO, EBRC, the following adjustments to the dossiers were agreed and prepared (specifics are available in Annexes 1 and 2 at the end of this document). Where relevant, adjustments made to the Ag dossiers submitted in 2010 will also be incorporated in Ag dossiers in preparation.

The relevant PMC Lead Registrants, Chairpersons, and Secretariat have been involved in or informed of all adjustments and support these:

Table 1. Summary of changes to the 2010 Ag dossiers

Substance	Deliverable	By	Comments/Rationale	Status/ Timinig
Silver metal	Remove TP for 90d study	EBRC	TP was included as part of a grouping approach, not necessary any more: · Inhalation: no longer a data gap; DNEL based on SCOEL OEL (which is based on human data), supported by very recent published 90-day rat inhalation study with nano-Ag (NOAEL=0,13 mg/m³) and discussion on particle size/dustiness of conventional µm sized Ag · Oral: Not a data gap, use (worst case) studies by Kim *et al.* with nano Ag (also used for current DNEL derivation)	end Feb. (IUCLID update)
	Revised DNEL derivation	EBRC	DNELs will not be changed. The point that the new nano inhalation study supports the current OEL will only be made in the endpoint record on the nano study. The separate report on DNEL derivation did not mention the testing proposal. The DNEL report was only edited to also cover AgCl which is due next for registrations. Figures/content were not changed.	-
Ag2O	Remove TP for 90d study	EBRC	Testing proposal removed. 90-day study formally not needed. However, a 28-days study is required for 10-100 t/a. Thus, for the sake of consistency, the Ag2O dossier will utilise the same data as Ag metal (see above), with read-across arguments.	end Feb. (IUCLID update)
AgNO3	Removed TP for 90d study (oral) with soluble Ag compound	EBRC	Testing proposal removed. Most recently, we became aware of an on-going full 90-day oral study with silver acetate by US NTP/FDA. Information on this on-going study will be included in the dossier with read-across justification from acetate to nitrate and justification that oral is most appropriate route. Note that the dossier will have to be updated once more, as soon as the NTP has published the final results (expected late 2012/2013).	end Feb. (IUCLID update)
Ag, Ag2O and AgNO3	Remove Aecom soil testing proposal	WCA	Testing completed	end Feb. (IUCLID update)

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Substance	Deliverable	By	Comments/Rationale	Status/ Timinig
Silver metal and AgNO3	Draft robust summaries of Aecom studies	WCA	Testing completed	Ongoing end Feb. (IUCLID update)
	Revised PNEC soil derivation	WCA	Need to explain why we are not using Aecom results. PNEC would be below regional background levels.	ongoing
	New TP for CSIRO soil work	WCA	Explain why more testing is needed, based on expert assessment (next line)	ongoing
	Expert review of Aecom work	CSIRO	Explain why more testing is needed (Aecom data not usable, tentative PNEC derived, Aecom PNEC < background levels)	Draft received
	Draft summary CSIRO feasibility study	CSIRO	Demonstrate that concept of bioavailability correction/ageing works	ongoing
	Update IUCLID accordingly	All		end Feb.
	Update CSR accordingly	All		end Feb.
	Review third party studies Add to IUCLID file	EBRC	Studies considered not relevant	Done end Feb.

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Cost of Ag dossiers update

The cost to preparing the updates to the Ag dossiers is of around 50 000 €; estimates are detailed below. Once all 2011 expenses are properly recorded by the Accountant, PMC will determine whether the available PMC reserves for the Ag project are sufficient to cover for these costs or whether a proposal for additional funding in the PMC 2012 invoices should be foreseen.

Table 2. Cost estimates for preparation of Ag dossier updates by end Feb 2012

Testing proposal	Item	Tasks involved	Cost	Total per TP
90 d Oral toxicity	EBRC	• drafting initial responses to ECHA • conference call with ECHA • monitoring additional testing • revising the read-across strategy appropriately • review of new study reports • updating the IUCLID files and the CSR accordingly	~ 20 000 €	~ 35 000 €
	Inhalation study	• performing study to determine feasibility to generate stable test atmosphere • performing acute inhalation study to fill data gap in dossiers	~ 15 000 €	
Soil toxicity	WCA	• justifying why existing soil data cannot be used • Update testing proposal • updating the IUCLID files and the CSR accordingly	~ 2000 €	~ 11 500 €
	CSIRO	• drafting of an expert opinion to put the previous soil data by Aecom into a wider context	~ 9500 €	
TOTAL				**~ 46 500 €**

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Annex 1
Further details on adjustments to the human health content of the Ag dossiers submitted in 2010
(for PMC Members' information)

Third party studies

- **Milliken studies:** a draft report is available upon request to PMC. EBRC have now reviewed the additional studies provided by third parties and have concluded that the data is not suitable for use in our dossiers. Studies were carried out with biocidal products designed for slow release of silver; these studies are relevant for their original purpose, but not for our purpose: the resulting silver concentrations were too low to derive no-effect levels for silver ions.
- **Older Russian paper, Smirnov, 1983:** considered not suitable. A number of short summaries were added to the IUCLID files, as the paper contained acute oral studies with several Ag substances, as well as repeat dose inhalation with AgNO3.

Inhalation study of Ag powder

Acute inhalation of Ag powder: In the 2010 dossier we had waived this. A technical feasibility study with Ag2O had shown that it was practically impossible to generate a test atmosphere with Ag2O. We had argued based on particle size, dustiness and density comparisons that this would also be the case for Ag metal powder.

Repeated dose inhalation: We had waived this as well, referring to the acute study. However, during the evaluation of the testing proposals ECHA has picked this up, and did not believe this comparison between Ag and Ag2O was justified. We had also already argued that the oral route is more relevant, since inhaled Ag powder material (if any) would mostly deposit in the upper respiratory tract and be translocated to the gastro-intestinal tract. However, this argumentation may not have been documented in sufficient detail. In consequence, ECHA had suggested that a repeat dose inhalation study with Ag metal should be considered.

Recent developments:
- We have conducted a feasibility study with silver powder, similar to what we did for disilver oxide. Surprisingly, the test results demonstrate that it is indeed possible to generate a stable test atmosphere for silver powder at a sufficiently high dose. Given the new data from our new feasibility study, we have no reason to defer this acute test. As agreed with the MC and the LRs, we have commissioned an acute inhalation study with silver powder with LPT in Hamburg, Germany (cost 15 000 €). A dossier update will be required, once this study becomes available (draft report including the histopathological results is scheduled for second week in May 2012). The current dossier will note that acute inhalation testing is on-going.
- repeated dose inhalation is no longer considered a data gap, since we can use the recently published 90-day inhalation study with nano-silver in support of the current DNEL. We have further extended the argumentation that in actual fact the oral route is more relevant for silver (of conventional µm sizes).

Testing proposal AgNO3 dossier

The US NIEHS and FDA are currently conducting a 13 weeks repeated dose study with rats on silver acetate (up to 400 mg/kg) under the NTP scheme. The study director is Dr Mary Boudreau of FDA. We were going to propose a 90 d study on silver acetate in our silver nitrate dossier (the nitrate cannot be tested since it is corrosive) but we can now use this on-going study to remove our testing proposal for a 90 d study in the silver nitrate dossier.

According to the Study Director the results will be made publicly available (on their website and in the peer reviewed literature). This means that most likely we will not need to negotiate the right to access the data. This will result in significant savings in cost and time. The exact time of publication is not confirmed though so PMC is not in a position to inform ECHA about the time at which the Ag dossier(s) could be further updated with the results of this on-going work.

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Annex 2

Detailed feed-back on adjustments to the environmental content of the Ag dossiers submitted in 2010
(for PMC Members' information)

Since the soil toxicity study data obtained by Aecom finds very low no-effect levels that are below the background concentrations, we cannot use the data in our dossier. On the other hand, the data is generated according to accepted OECD protocols and we cannot dismiss the data either.

We therefore need to find a way to deal with the data from Aecom as well as with the results of CSIRO's preliminary findings in our dossier.

To address this, in the dossier update we will therefore:
- remove the testing proposal for the Aecom work
- report the actual Aecom data in IUCLID
- provide an expert assessment (by CSIRO) putting the Aecom data in a larger context and explaining why more data is needed. A draft report from CSIRO is available upon request. It explains very well the limitations of the Aecom studies and makes a convincing case why more work is needed.

Next steps involve:
- WCA will provide a revised PNEC derivation where they refer to the CSIRO expert assessment and explain why the Aecom data cannot be used. The (tentative) PNEC soil will remain unchanged for the time being.
- Initial data from CSIRO will be reported as a 'pilot/feasibility study', carried out to demonstrate the concept that bioavailability correct/ageing/leaching has a significant influence on silver's toxicity to soil. A report is expected by mid-Feb.
- Draft a revised Testing Proposal: data from the CSIRO pilot study will be used in the Testing Proposal to explain why the data gap can only be closed after more data have been generated (we want to avoid that ECHA forces us to use the no-effect-levels from the Aecom study which are not realistic/reasonable). This is still ongoing.

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