



MISA Workplan following Human Health Workshop (2 October 2018)

INTRODUCTION

A first MISA workshop was held in Brussels (Metals Conference Center, 2 October 2018). This workshop focused on human health endpoints, and more specifically on:

- Read-across,
- EOGRTS/Route of Exposure, and
- Mutagenicity.

Following the workshop and the discussions and learning lessons, the EPMF (European Precious Metals Federation) has identified several actions for its substances (cfr. www.epmf.be for an overview).

More details are provided on the next pages including specifications of the concerned substances and actions, and an indicative timing for updating the dossiers.

For further questions, please contact Mss France Capon (france.capon@epmf.be) or Mr Jelle Mertens (jelle.mertens@epmf.be).



WORKPLAN

Topic	Substances covered		Comments	Timeline
	Name	CAS		
Read-Across				
Palladium – Revise category approach and redraft Read-Across justification reports (according to RAAF criteria)	Palladium monoxide	1314-08-5	EPMF is currently performing additional short-term assays and 28-d RDT/Repro screening studies to improve the mammalian toxicity database. Once this test data is available, the dossiers will be updated, the category approach will be revised and RAJRs will be redrafted where appropriate. Several actions have been identified: -include test data in datamatrix -clearly determine category boundaries -show speciation to similar ‘toxicological active species’ -show absence of counter-ion effects -verify proper use of bioelution data -include at least test data of the worst-case category member per category -read-across of information to all category members.	Mammalian toxicity testing: today - Q3 2019. Revise category approach and (re)draft RAJR: Q3-4 2019. Update relevant registration dossiers: Q4 2019.
	Palladium dihydroxide	12135-22-7		
	Palladium dichloride	7647-10-1		
	Disodium tetrachloropalladate	13820-53-6		
	Dihydrogen tetrachloropalladate	16970-55-1		
	Dipotassium tetrachloropalladate	10025-98-6		
	(Trans)diamminedichloropalladium	13782-33-7		
	Tetraamminepalladium(II) diacetate	61495-96-3		
	Tetraamminepalladium(II) dichloride	13815-17-3		
	Tetraamminepalladium(II) hydrogen carbonate	134620-00-1		
	Dipotassium hexachloropalladate(IV)	16919-73-6		
	Diammonium hexachloropalladate(IV)	19168-23-1		



<p>Platinum - Draft Read-Across justification reports (according to RAAF criteria)</p>	<p>Dihydrogen hexahydroxyplatinate ('HHPA') Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2) ('HHPA-2AE')</p>	<p>51850-20-5 68133-90-4</p>	<p>Read-across is included in testing proposal for in vivo mutagenicity testing. However, no RAJR has been drafted yet. This is currently under development, and will be drafted according to the RAAF requirements.</p>	<p>Include RAJR in HHPA (target substance) registration dossier when in vivo testing is finalised. ECHA is currently assessing the TP, and the registrants are waiting the draft decision. Further timing dependent on the regulatory assessment processes.</p>
<p>PGMs plus Gold – Update dossier including Read-Across justification reports (according to RAAF criteria)</p>	<p>Platinum Palladium Ruthenium Rhodium Iridium Rhodium Gold</p>	<p>7440-06-4 7440-05-3 7440-18-8 7440-16-6 7439-88-5 7440-16-6 7440-57-5</p>	<p>EPMF is currently running a literature review for mammalian toxicity data of the Platinum Group Metals plus gold (metallic form). Based on the outcome, proper use of bioelution will be investigated, and mammalian toxicity endpoints will be updated where required (including RAJR where needed).</p>	<p>EPMF Literature review: Q4 2018. Review of dossiers: Q1 2019. Subsequent timing unclear, as this depends on the identified data vs use of bioelution data. Therefore, three timings for dossier updates are indicated: -if all endpoints are adequately covered: Q2 2019 -if further in vitro/acute mammalian tox testing is required: Q3-4 2019 -if further RDT/Reprotox screening testing is required: Q2-3 2020</p>



				Note that each metal might have a different timing depending on data availability and data requirements.
<i>Rhodium - Draft Read-Across justification reports (according to RAAF criteria)</i>	Dirhodium trisulphate Rhodium trichloride,hydrate Rhodium trinitrate Rhodium (III) acetate	10489-46-0 20765-98-4 10139-58-9 42204-14-8	A testing proposal for in vivo mutagenicity testing is under development, together with a RAJR for the proposed target substances. The RAJR will be drafted according to the RAAF requirements.	Include TP and RAJR in Dirhodium trisulphate (source substance) registration dossier: Q4 2018.
<i>Silver – investigate grouping + Draft Read-Across justification reports (according to RAAF criteria)</i>	Silver Silver nitrate Disilver oxide Silver carbonate Disilver(1+) sulphate Silver chloride Silver bromide Silver iodide	7440-22-4 7761-88-8 20667-12-3 534-16-7 10294-26-5 7783-90-6 7785-23-1 7783-96-2	Read-across is applied for mammalian toxicity endpoints, including in the TP for EOGRTS. Bioelution is used as a 1 st tier tool to justify grouping, but current data are considered insufficient by the registrants. A 2-tiered approach will be applied to re-investigate and properly justify grouping: -tier 1: literature review of available in vivo TK data + perform bioelution testing in artificial gastric and intestinal liquids -tier 2: in vivo TK testing with selected Ag substances (tier 2 depends on outcome tier 1). No RAJR has been drafted yet, but will be drafted once the category approach of	Literature review of available TK data + additional bioelution testing: Q4 2018-Q1 2019. In vivo TK testing (if needed): Q1-2 2019). Draft RAJR and include in dossiers: Q2-3 2019.



			the various Ag substances has been properly developed.	
EOGRTS / Route of Exposure				
Testing proposal EOGRTS	Silver Silver nitrate Disilver oxide Silver carbonate Disilver(1+) sulphate Silver chloride Silver bromide Silver iodide Karstedt Concentrate	7440-22-4 7761-88-8 20667-12-3 534-16-7 10294-26-5 7783-90-6 7785-23-1 7783-96-2 68478-92-2	A TP for EOGRTS is included in the silver dossiers, and the dossier of Karstedt Concentrate. Once the final decision is taken, the testing will be conducted (if approved). The dossiers will be updated, and appropriate actions will be taken (where required). The learnings of the MISA workshop will be considered during testing.	ECHA is currently assessing the TP, and the registrants are waiting the draft decision. Further timing dependent on the regulatory assessment processes.
All substances – revision of uses/procs	All EPMF dossiers (cfr. https://www.epmf.be/)		Selected PROCs by registrants are used as (co-)decisive criterion for identification of the most appropriate exposure route for mammalian toxicity testing. Uses and PROCs of all dossiers submitted by EPMF will be revised and updated where needed.	2019 for Ag and Pd substances. 2020 for Pt, Rh and Ru substances. For efficiency reasons, dossiers will only be submitted when all individual issues are updated.
Mutagenicity				
Testing proposal in vivo mutagenicity	Diammonium hexachloroplatinate Hexachloroplatinic acid Dipotassium hexachloroplatinate	16919-58-7 16941-12-1 16921-30-5	A TP for in vivo mutagenicity is included in the dossiers. Once the final decision is taken, the testing will be conducted (if approved). The dossiers will be updated,	ECHA is currently assessing the TP, and the registrants are waiting the draft decision. Further timing dependent on



Tetraammineplatinum dichloride	13933-32-9	and appropriate actions will be taken (where required). The learnings of the MISA workshop will be considered during testing.	the regulatory assessment processes.
Tetraammineplatinum dinitrate (in solution)	20634-12-2		
Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2)	68133-90-4		
Dihydrogen hexahydroxyplatinate	51850-20-5		
Platinum dinitrate (UVCB)	18496-40-7		
Dipotassium tetrachloroplatinate	10025-99-7		
Potassium dicyanoargentate	506-61-6		
Potassium dicyanoaurate	13967-50-5		