



MISA Workplan following Human Health Workshop (2 October 2018) – Status update August 2019

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.

A status update has been added in a separate row below each action.

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 | |
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| | Name | CAS | | | |
| <i>Read-Across</i> | | | | | |
| 1 | <i>Palladium – Revise category approach and redraft Read-Across justification reports (according to RAAF criteria)</i> | Palladium monoxide Palladium dihydroxide Palladium dichloride Disodium tetrachloropalladate Dihydrogen tetrachloropalladate Dipotassium tetrachloropalladate (Trans)diamminedichloropalladium Tetraamminepalladium(II) diacetate Tetraamminepalladium(II) dichloride Tetraamminepalladium(II) hydrogen carbonate Dipotassium hexachloropalladate(IV) Diammonium hexachloropalladate(IV) | 1314-08-5 12135-22-7 7647-10-1 13820-53-6 16970-55-1 10025-98-6 13782-33-7 61495-96-3 13815-17-3 134620-00-1 16919-73-6 19168-23-1 | 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 RAJR's 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 | Mammalian toxicity testing: today - Q3 2019. Revise category approach and (re)draft RAJR: Q3-4 2019. Update relevant registration dossiers: Q4 2019. |



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| | Palladium(II) di(4-oxopent-2-en-2-oate) | 14024-61-4 | -include at least test data of the worst-case category member per category -read-across of information to all category members. | |
| STATUS Aug 2019 | <p>Sub-chronic mammalian toxicity assays: Palladium(II) di(4-oxopent-2-en-2-oate) - OECD422 assay Full assay: in-life phase finalised Draft report expected Dec 2019 Disodium tetrachloropalladate - OECD407/421 assays Dose-Range Finding ('DRF') assay finalised Analytics pending (scheduled for end summer - analytical problems) Full assay: anticipated initiation 2nd half 2019 Palladium dichloride - OECD407/421 assays Dose-Range Finding ('DRF') assay finalised Analytics finalised summer 2019 (analytical problems) Second DRF required for proper dose setting in full assays – DRF will be initiated 14 Oct 2019</p> <p>Acute mammalian toxicity assays Testing finalised, final reports available Individual dossiers will be updated when all actions per substance have been finalised (cfr. MISA ENV Workplan)</p> <p>Read-Across justification Reports:</p> | | | <p>Ongoing (dossier update scheduled Q1 2020)</p> <p>Ongoing (delay due to analytical problems – dossier update scheduled Q3/4 2020)</p> <p>Ongoing (delay due to analytical problems – dossier update scheduled Q4 2020)</p> <p>Done Ongoing</p> |



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| | | <p>Speciation to similar toxicologically active species Methodological challenges to detect & differentiate Pd complexes of interest, under discussion with member companies</p> <p>Absence of counter-ion effects Justification document being drafted under Eurometaux umbrella</p> | | | <p>Pending (internal discussions to find proper analytical techniques)</p> <p>Ongoing</p> |
| 2 | <p>Platinum - Draft Read-Across justification reports (according to RAAF criteria)</p> | <p>Dihydrogen hexahydroxyplatinate ('HHPA')</p> | 51850-20-5 | <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>Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2) ('HHPA-2AE')</p> | 68133-90-4 | | |
| | <p>STATUS Aug 2019</p> | <p>RAJR has been drafted</p> | | | <p>Done (dossier update foreseen after finalizing in vivo muta testing)</p> |
| 3 | <p>PGMs plus Gold – Update dossier including Read-Across justification reports (according to RAAF criteria)</p> | <p>Platinum</p> | 7440-06-4 | <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</p> |
| | | <p>Palladium</p> | 7440-05-3 | | |
| | | <p>Ruthenium</p> | 7440-18-8 | | |
| | | <p>Rhodium</p> | 7440-16-6 | | |
| | | <p>Iridium</p> | 7439-88-5 | | |
| | | <p>Gold</p> | 7440-57-5 | | |



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| | | | | | -if further in vitro/acute mammalian tox testing is required: Q3-4 2019 -if further RDT/Reprotox screening testing is required: Q2-3 2020 Note that each metal might have a different timing depending on data availability and data requirements. |
| | STATUS Aug 2019 | <p>Literature review finalised Dossiers reviewed internally, prioritization & way-forward agreed:</p> <p><u>Tier 1 dossiers</u> Platinum, Ruthenium: read-across possibilities under investigation – in vitro experimental work scheduled Q1 2020. Results of this testing will define if and what further testing is required. Palladium: read-across possibilities investigated – further in vitro/acute mammalian toxicity work scheduled Q1/2 2020 Iridium: experimental work scheduled Q3-4 2019</p> <p><u>Tier 2 dossiers</u> Rhodium and Gold – to be discussed internally</p> | | | <p>Done</p> <p>Ongoing (timing dossier update depends on findings in scheduled in vitro testing) Ongoing (dossier update scheduled Q2/3 2020) Ongoing (dossier update scheduled Q1 2020) Pending (delay due to internal prioritization)</p> |
| 4 | Rhodium - Draft Read-Across justification reports (according to RAAF criteria) | <p>Dirhodium trisulphate Rhodium trichloride,hydrate Rhodium trinitrate Rhodium (III) acetate</p> | <p>10489-46-0 20765-98-4 10139-58-9 42204-14-8</p> | <p>A testing proposal for in vivo mutagenicity testing is under development, together with a RAJR for the proposed target substances. The RAJR will be</p> | <p>Include TP and RAJR in Dirhodium trisulphate (source substance) registration dossier: Q4 2018.</p> |



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| | | | | drafted according to the RAAF requirements. | |
| | STATUS Aug 2019 | RAJR drafted TP included in dossier | | | Done (dossier resubmitted Feb 2019) |
| 5 | Silver – investigate grouping + Draft Read-Across justification reports (according to RAAF criteria) | 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 the various Ag substances has been properly developed. | 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. |



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| | STATUS Aug 2019 | Literature review finalised In vivo TK testing required – test design agreed, CRO contracted. RAJR will be drafted once category boundaries are clarified based on outcome in vivo TK testing. | | | Done Ongoing (dossier update < 3 Jan 2022 (cfr. timing action 6 - EOGRTS)) |
| EOGRTS / Route of Exposure | | | | | |
| 6 | 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. |
| | STATUS Aug 2019 | Silver and silver compounds: Final decision on TP received CRO for EOGRTS contracted, time slot for testing fixed Karstedt Concentrate: ECHA SID investigation triggered dossier update and generation new identifiers. New identifiers received from ECHA, dossier being updated (submission by LR < end August 2019) Investigation TP by ECHA expected to continue afterwards | | | Ongoing (dossier will be updated within legal deadline of 3 Jan 2022) Done Ongoing (timing dossier update for EOGRTS depends on timing ECHA/MS review) |



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| 7 | 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. |
| | STATUS Aug 2019 | Revision scheduled in line with anticipated timing of dossier updates | | | Ongoing |
| Mutagenicity | | | | | |
| 8 | Testing proposal in vivo mutagenicity | Diammonium hexachloroplatinate | 16919-58-7 | 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, 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. |
| | | Hexachloroplatinic acid | 16941-12-1 | | |
| | | Dipotassium hexachloroplatinate | 16921-30-5 | | |
| | | Tetraammineplatinum dichloride | 13933-32-9 | | |
| | | Tetraammineplatinum dinitrate (in solution) | 20634-12-2 | | |
| | | Dihydrogen hexahydroxyplatinate, compound with 2-aminoethanol (1:2) | 68133-90-4 | | |



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| | <p>Dihydrogen hexahydroxyplatinate 51850-20-5</p> <p>Platinum dinitrate (UVCB) 18496-40-7</p> <p>Dipotassium tetrachloroplatinate 10025-99-7</p> <p>Potassium dicyanoargentate 506-61-6</p> <p>Potassium dicyanoaurate 13967-50-5</p> | | |
| STATUS Aug 2019 | <p>Five TP included:</p> <p>Tetraammineplatinum compounds Final decision received CRO for in vivo assay contracted, test item selection ongoing</p> <p>Hexachloroplatinate compounds Revised draft decision received Comments to PfA being drafted and will be submitted by LR <16 Sept 2019</p> <p>Tetrachloroplatinate compounds Draft decision received November 2018</p> <p>Hexahydroxyplatinate compounds Public consultation finalised</p> <p>Platinum dinitrate ECHA SID investigation triggered dossier update and generation new identifiers Registrants waiting further input from ECHA</p> | | <p>Ongoing (dossiers will be updated within legal deadline of 15 July 2020)</p> <p>Ongoing (Timing of testing & dossier update depending on ECHA/MS review)</p> <p>Ongoing (Timing of testing & dossier update depending on ECHA/MS review)</p> <p>Ongoing (Timing of testing & dossier update depending on ECHA/MS review)</p> <p>Ongoing (Timing of testing & dossier update depending on ECHA/MS review)</p> |