Committee for Risk Assessment

RAC

Annex 4
Records
of the targeted consultation following the submission of a final comparative toxicokinetic study as well as a 90-day repeat dose toxicity study, a EOGRTS and its preliminary study on silver acetate

Silver

EC Number: 231-131-3
CAS Number: 7440-22-4

CLH-O-0000007152-82-01/F

Adopted

2 June 2022

ANNEX 4- RECORDS OF THE TARGETED CONSULTATION FOLLOWING THE SUBMISSION OF A FINAL COMPARATIVE TOXICOKINETIC STUDY AS WELL AS A 90-DAY REPEAT DOSE TOXICITY STUDY, A EOGRTS AND ITS PRELIMINARY STUDY ON SILVER ACETATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of silver (EC 231-131-3; CAS 7440-22-4) was submitted by Sweden and was subject to a consultation, which ended on 18/12/2020. The comments received by that date are compiled in Annex 2 to the opinion.

A previous ad hoc consultation was held on a preliminary summary of a new, at the time partly still ongoing in-vivo comparative Toxicokinetic Study provided by the European Precious Metals Federation (EPMF) on silver acetate (AgAc), and silver nitrate (AgNO3), one Agsilver nanoparticles (AgNP) and a sub-micron size powder-form (AgMP) of bulk elemental silver (on 06/07/2021 to 20/07/2021). The second ad hoc consultation was on the final comparative toxicokinetic study as well as on a 90-day study, EOGRTS and its preliminary study on silver acetate that were finalised and provided to ECHA during the CLH process of silver after the consultation of the CLH dossier. The second ad hoc consultation also covered additional literature studies that are included in the assessment of developmental neurotoxicity and neurotoxicity by RAC during the CLH process. The second ad hoc consultation was launched from 03/05/2022 to 17/05/2022 and the comments received are listed below.

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: silver
EC number: 231-131-3
CAS number: 7440-22-4
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2022	Poland	<confidential>	Company-Manufacturer	1
Comment received				
In connection with the defense of nanosilver, we enclose the tests we conducted in accordance with OECD 439 and OCED 428 (added to the appendix). These tests confirm the lack of skin irritation and the lack of penetration of nanosilver aXonnite through the epidermal barrier, and thus the lack of potential for effects on the human body. Genotoxicity testing, conducted at one concentration (highest concentration), showed no geno- or cytotoxic effects in a metabolic simulation model. The lack of penetration through the epidermal barrier, lack of irritation and genotoxicity even at high concentrations is, in our opinion, sufficient confirmation of the absence of systemic effects, including toxicity. We remind you that aXonnite Silver is 99.99% pure silver particles suspended in demineralized water without any additives such as surfactants, acids or polymers. Reports of possible genotoxic effects of nano silver				

presented in the literature are often due to poor methodology or analysis of test results or tests performed on ionic silver or silver with necessary stabilizing substances. Water-soluble silver or silver salts such as silver nitrate, silver acetate, which were included in the CLH report, are also not pure silver but are considered when evaluating pure silver. They are silver salts and just as we cannot compare metallic sodium with its salt, e.g. sodium chloride, in this case we cannot even talk about nanomaterial when we talk about silver salt. It is important to mention that the very definition of nanomaterial talks about solid, insoluble or bio-soluble particles, so silver salts, although rated as silver in the CLH report, do not meet the definition of nanomaterial.
In the documents found at this link Additional information report Silver_Reproductive toxicity, Additional information report Silver_STOT RE, Additional information report Silver_Toxicokinetics, the forms and purity of nano and micro silver are not clearly presented (no raw material characterization), additionally the reports focus mainly on silver salts and compounds that are soluble. If substances are biosoluble the possibility of their action and availability in the body is very limited, harmfulness is difficult to assess. Despite the low potential for accumulation in the document Additional information report Silver_Toxicokinetics during oral exposure was not noted disruptive effects on the body or effects on its homeostasis as was the case for silver ions. It should be emphasized that the evaluation of silver as a cosmetic raw material should be performed in transdermal exposure.
We would like to stress again that silver should also be evaluated as nano silver, in our case as a suspension of pure metallic unstabilized silver in demineralized water.
Please see comments contained directly in the documents: Additional information report Silver_Reproductive toxicity, Additional information report Silver_STOT RE, Additional information report Silver_Toxicokinetics, CLH Report

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2022-04-29_Additional information report Silver_Toxicokinetics.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment LAB TEST_1.zip

RAC's response

Thank you. Please see the RAC opinion for the assessment of toxicokinetics and conclusions on hazard classifications. Please note that for systemic hazard classes also other routes of exposures are relevant, principally oral and inhalation routes in addition to the dermal route of exposure.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2022	United Kingdom		Individual	2

Comment received

This is a contribution for Professor Len Levy making a number of general points noting that: (1) a number of metal compounds, including a silver soluble silver compounds, may cause secondary effects via perturbation of some essential metals, which in turn can lead to harmful effects (e.g., reproductive outcomes) as shown here and (2), where comparative toxicokinetics data is available as here) then this can be used to give far more informative and targeted hazard and risk assessment decisions for less soluble/bioavailable members of the same metal group where dose-effect related endpoints occur. This will encourage the collection and more intelligent use of toxicokinetic data.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ECHA Consulation - Silver_Final 2.docx
RAC's response
Thank you. In the CLH process, RAC is obliged to consider the data included in the CLH report and provided during the consultation.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2022	United Kingdom		Individual	3
Comment received				
see general comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment ECHA Consulation - Silver_Final 2.docx				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2022	Sweden		MemberState	4
Comment received				
General: The results from the EOGRTS study clearly shows that the silver ion causes effects on haematological parameters, ALP activity, cholesterol levels, cardiac and thymic weight changes, reduced live birth rate, pup viability, reduced pup growth and failure to thrive - effects also noted in a two-generation study with silver zinc zeolite and to varying extent in studies with other silver substances releasing silver ions. The results for the DNT cohort included in the EOGRTS further demonstrate brain myelinopathy, cell loss, diminution of the size of the hippocampus and deficits in motor function and neurobehavioural parameters. Similar investigations on the developing neural system were not included in the study with silver zinc zeolite. As extensively discussed in the report, effects are likely due to silver interfering with and structurally deforming ceruloplasmin leading to a copper deficiency in the foetus causing pre-term death or failure to thrive in pups surviving delivery. This may indeed be the principal mode of action for the intrinsic toxicity of the silver ion and is an important piece of information to support classification and labelling to ensure protection of women from exposure during pregnancy and thus avoid any risk. The copper deficiency caused by silver is a specific effect representing the mode of action of the substance and should not be considered an unspecific secondary effect. Since the blood circulation is shared with the foetus during pregnancy, a structural deformation of ceruloplasmin and reduced capacity of copper binding in the mother would likely affect the unborn child before effects of the copper deficiency manifest in the mother. Results from a toxicokinetic study (individual data not available) indicate that the silver ion release from bulk silver is less than from nano and soluble silver resulting in 2-3 times lower tissue levels and the EPMF thus argues that the effects observed in the study with silver acetate are not relevant for silver in bulk and nanoform. The dossier submitter does not support this line of reasoning since, for this endpoint and for all substances, severity of effects commonly depends on the level of exposure. However, classification and labelling is based on the intrinsic property of a substance and				

this data, as well as data for other silver-releasing substances, clearly show that effects observed represent an intrinsic property of the silver ion, regardless from which silver substance it is released. Moreover, there is no comparable fertility study for silver in bulk or nanoform, demonstrating a lack of similar effects or unaffected levels of copper in pups. Therefore, it is not considered safe to conclude that this intrinsic property of the silver ion is not relevant for silver in bulk and nanoform. Especially taking into account that there is no evidence demonstrating that copper deficiency is the sole mode of action for the silver ion toxicity observed with respect to viability, cardiac effects, effects on the thymus and the neuropathological and neurobehavioral effects observed in the offspring brain. In conclusion, we consider the new information to support the classification for reproductive toxicity proposed in the CLH report and to provide the information needed to support classification for STOT-RE based on toxicity to the nervous system. General: In the absence of a full study report with tabulated mean values for parameters investigated and with individual data, it is not possible to independently assess effects observed. For example, the information on effects on testis weight, spermatid and cauda epididymis sperm counts without effects on motile, progressive, motion and morphology cannot be verified. Additional information report, page 42: As recognized by EMPF the embryofetal and neonatal blood-brain barrier may be more permeable than the adult BBB. The results from the toxicokinetic study show that silver is detected in the brains of adult females and males exposed to silver nitrate as well as silver in nano- and micro-size form. There is no evidence demonstrating that silver ions that penetrate the blood-brain barrier would be quickly sequestered into ultraslow solubility selenide ad sulphide complexes. This is only a speculation.
RAC’s response
Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2022	Sweden		MemberState	5
Comment received				
Please see the comment on reproductive toxicity.				
RAC’s response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2022	Poland	<confidential>	Company-Manufacturer	6
Comment received				
Scan raportEN 09.02.2022, non skin penetration ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2022-04-29_Additional information report Silver_Toxicokinetics.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment LAB TEST_1.zip				

RAC's response
Thank you for the report. Please note that for Specific Target Organ Toxicity also other routes of exposures are relevant, principally oral and inhalation routes in addition to the dermal route of exposure.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2022	United Kingdom		Individual	7
Comment received				
see general comments ECHA note – An attachment was submitted with the comment above. Refer to public attachment ECHA Consulation - Silver_Final 2.docx				
RAC's response				
Thank you for the comment.				

PUBLIC ATTACHMENTS
1. 2022-04-29_Additional information report Silver_Toxicokinetics.zip [Please refer to comment No. 1, 6]
2. ECHA Consulation - Silver_Final 2.docx [Please refer to comment No. 2, 3, 7]

CONFIDENTIAL ATTACHMENTS
1. LAB TEST_1.zip [Please refer to comment No. 1, 6]