

## COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. 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.

**Last data extracted on 13.11.2023**

**Substance name: silver nitrate**

**CAS number: 7761-88-8**

**EC number: 231-853-9**

**Dossier submitter: Sweden**

### GENERAL COMMENTS

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Country | Organisation           | Type of Organisation | Comment number |
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| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | France  | SCHNEIDER ELECTRIC SAS | Company-Manufacturer | 1              |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |                        |                      |                |
| <p>Schneider Electric is a technology company providing energy and automation digital solutions for efficiency and sustainability for our customers around the world. We are a 34-billion-euro revenue company with 135,000 employees in over 100 countries and our key businesses are Energy management and Industrial Automation. Silver Nitrate is used in one of our manufacturing processes to produce silver metal, part of some products in our portfolio. We always considered chemical risk management as key fundamentals of our due diligence towards our workers, customers, and the environment. As an electrical company, we don't pretend having strong enough skills in toxicology to argue against what is proposed and we will follow the conclusions of the final decision.</p> <p>Nevertheless, in case of classification modification, we want to push for a global and synchronized worldwide harmonized classification to avoid competitive issues in case of differences around the world that would penalize European industry.</p> |         |                        |                      |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Country | Organisation                        | Type of Organisation          | Comment number |
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| 08.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Belgium | European Precious Metals Federation | Industry or trade association | 2              |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                     |                               |                |
| <p>The European Precious Metals Federation (EPMF) welcomes this opportunity to provide feedback to the CLH report for Silver nitrate (EC 231-853-9; CAS 7761-88-8).</p> <p>The EPMF has closely considered the proposal for Harmonised Classification and Labelling prepared by the Swedish Chemicals Agency (KEMI). The data assessment and proposed classification entries have been compared with the previous assessments of the Risk Assessment Committee (RAC) for Silver Zinc Zeolite (CAS 130328-20-0; adopted 4 December 2015) and Silver Metal (EC 231-131-3; CAS 7440-22-4; adopted 2 June 2022) and the EU-REACH dossier for silver nitrate.</p> <p>In summary, the EPMF provides feedback on:</p> <ul style="list-style-type: none"><li>• Identified uses: the listed uses for silver nitrate did not consider the uses reported under EU REACH. Under EU REACH, silver is reported to be used as a.o. intermediate in the</li></ul> |         |                                     |                               |                |

production of other silver substances, laboratory reagent or in coating. More details are available on the ECHA Dissemination website.

- Data sources\*
- Oxidising solids\*
- Corrosive to metals: based on industrial experience, silver nitrate is self-classified as Corrosive to Metals (Metal Corr. 1; H290) under EU-REACH. Industry experienced corrosion to metallic containers made of e.g. zinc, copper, iron or aluminium, but not to e.g. stainless steel. This is mainly the case for silver nitrate solutions. However, also for solid forms, corrosion might take place in presence of air humidity.
- Toxicokinetics\*
- Acute toxicity – oral\*
- Acute toxicity – inhalation\*
- Skin corrosion/irritation\*
- Eye Damage: based on the evidence from an old in vivo skin corrosion assay and confirmed by the more recent in vitro skin corrosion testing, silver nitrate has been self-classified as Eye Damage 1 (H318) under EU-REACH. This is in line with the classification proposed in the CLH Report for silver nitrate (cf. section 10.5), although this classification is not included in the overview tables in section 2.1 of the CLH Report.
- Skin sensitisation\*
- Germ cell mutagenicity\*
- Carcinogenicity: the EPMF would like to inform about an ongoing OECD453 and GLP compliant study with silver acetate (Charles River Den Bosch, NL). The in-life phase will be terminated in November-December 2023 and a draft report is expected mid-2024. This study will inform about the carcinogenic potential of silver acetate and, via read across, also silver nitrate.
- Reproductive toxicity\*
- Specific Target Organ Toxicity-Repeated Exposure\*
- Environmental transformation\*
- Bioaccumulation\*
- Acute Aquatic hazard\*
- Chronic Aquatic hazard\*

More details for each of the hazard classes cited above and marked with an '\*' are provided in the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate\_EPMFcmts\_final\_231107.pdf

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country | Organisation | Type of Organisation | Comment number |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 09.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Germany |              | MemberState          | 3              |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |              |                      |                |
| The comprehensive statement of used data sources is highly appreciated. The DE-CA agrees that in light of new comparative kinetic data the soluble salts represent the worst case of silver ion release and thus data with nanoforms can be used if adverse effects are observed. Uncertainties around induction of ROS and oxidative stress by nanoparticles as compared to silver ions as well as accumulation of nanoparticles with concentrated release of silver ions in one location should be taken into account. However, both of the scenarios could serve as worst-case assumptions and effects observed should be considered for hazard assessment of silver nitrate as well. |         |              |                      |                |
| Please note a mistake in the last sentence of Section 9.1 of the CLH report. It states that generally "oral absorption rarely exceeds dermal absorption" when in fact the opposite is                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |              |                      |                |

true (dermal absorption is generally considered to be lower than oral absorption, c.f. Chapter R.8 of the Guidance on REACH information requirements, p.19: “in general, dermal absorption will not be higher than oral absorption”). However, using the default value of 5 % for both routes appears reasonable based on the available data.

Table 6:

In the labelling proposal, GHS07 should be removed and the presentation of the ATE should be adapted according to Annex VI (oral: ATE = 29 mg/kg bw).

| Date       | Country | Organisation                        | Type of Organisation          | Comment number |
|------------|---------|-------------------------------------|-------------------------------|----------------|
| 10.11.2023 | Belgium | European Biocidal Silver Task Force | Industry or trade association | 4              |

Comment received

Section 5 – Identified Uses: The attached document (page 1) explains that, in the categories shown where silver nitrate is used directly as an active substance, the concentrations used are very low.

Section 6 – Data Sources: The attached document (page 1) explains that basing conclusions only on effects attributed to the silver ion in studies conducted with different silver salts is not sufficient to classify silver nitrate without significant uncertainty. Silver nitrate is a corrosive substance and as such has toxicological properties that are significantly different to other silver salts and silver containing substances.

Section 9.1 (Dermal Toxicokinetics) – The attached document (pages 2-3) explains that, based on weight of evidence from several published papers and the opinion of regulators, a dermal absorption value of 0.1% is appropriate for systemic exposure to silver following dermal contact. The document highlights key observations of the Scientific Committee on Consumer Safety (SCCS) from their 2016 review of silver-based material under the Cosmetics Regulation (EC) No 1223/2009.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silver nitrate CLH STF comments - 10 November.pdf

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 10.11.2023 | Belgium | Umicore      | Company-Importer     | 5              |

Comment received

We would like to comment on the Proposal for Harmonized Classification and Labelling for Silver nitrate (EC 231-853-9; CAS 7761-88-8).

These comments are submitted on behalf of the Umicore group including the following legal entities: Umicore NV/SA, Agosi AG, Österreichische Gold- und Silber-Scheideanstalt Ges.m.b.H and Todini Deutschland GmbH.

Umicore is a global materials technology and recycling group serving a wide range of industries. At Umicore we import and use silver nitrate for many applications.

In Hoboken, the Umicore Precious Metals Refining (Umicore NV/SA) operates as one of the world's largest precious metals recycling facilities. This business unit of Umicore is the world market leader in recycling complex waste streams containing precious and other non-ferrous metals.

Silver nitrate is an irreplaceable intermediate in our precious metals flowsheet, as it facilitates the separation between silver and PGM refining.

The Business Unit JIM (Jewelry and Industrial Metals) precious metal produces standard and special products from precious metals, semi-finished or near-end, precious metal based alloys for industrial applications and crafts. Precious metals are recycled from various scrap materials and made available for production.

At Agosi AG, silver nitrate is used as electrolyte in the electrowinning with two separated processes as essential parts of the silver refining process. The refining of silver is the most important precious metals recycling process part at the Agosi AG. There is no substitution of silver nitrate in the silver refining process possible.

At Österreichische Gold- und Silberscheideanstalt Ges. m.b.H silver nitrate in solution is part of the precious metals recycling process.

Umicore Cobalt & Specialty Materials is a worldwide leader in the recycling, refining, transformation and marketing of metal-based specialty chemicals, with a main focus on cobalt and nickel. Their broad expertise covers a multitude of applications in both chemicals and powder metallurgy. As part of the Cobalt & Specialty Materials unit, a trading branch named Todini focuses on worldwide reselling of metal-based specialty chemicals both from internal and external sources to a variety of applications. The entity Todini Deutschland GmbH is active in trading of Silver nitrate, with its main downstream user applications being the production of mirrors, textiles (silver nitrate is used for its antiseptic properties) or for surface treatment and chemical analyses and synthesis.

Silver nitrate is often, as it is in Umicore, processed as part of the wider precious metals refining process, therefore changes to the classification of silver nitrate could have negative knock-on effects on the entire precious metal refinery sector and refining processes put in place.

If uses of silver nitrate would be reduced, this would be translated first in a cost of refining silver, and potentially triggering a non-recycling of some materials (which may be then landfilled instead of recycled), to finally a reduction of precious metals found in the incoming material. Ultimately this would impact manufacturers/importers and would break the closed recycling loop that is currently in place.

Umicore supports the scientific comments submitted by the European Precious Metals Federation (EPMF). In the comments below (on the open hazard classes), we share some of the key messages and arguments addressed in EPMF's submission.

In addition of the comments on the open hazard classes, we also would like to comment on the data sources used in the CLH proposal.

The selection of studies for the hazard assessment of silver nitrate should consider only relevant and reliable studies. As detailed in the CLH Report for silver nitrate, the silver ion is considered the relevant toxic moiety for mammalian and environmental endpoints. Data from silver metal (incl. nanosilver) and other Silver Containing Active Substances should not be used. This is extensively explained in EPMF's submission.

In the uploaded attachment, you can find a summary of our position and the classification of silver nitrate supported by Umicore.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf

## PHYSICAL HAZARDS

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 6              |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details are provided in the attached document.                                                                                     |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country | Organisation | Type of Organisation | Comment number |
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| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Belgium | Umicore      | Company-Importer     | 7              |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |              |                      |                |
| <p>Oxidising solids: Experimental data are available for test items with various particle sizes. These data suggest that particle size plays an important role in the classification for this endpoint with finer materials being more potent oxidizers than courser materials. The currently included classification entry under EU-REACH includes a conservative cut-off size to distinguish between Oxid. Solid 1 (D10&lt;250 µm) and Oxid. Solid 2 (D10&gt;250 µm). The EPMF however acknowledges that this assessment is based on a limited amount of experimental data. Therefore, additional testing is currently ongoing to clarify and/or refine this classification. The re-assessment of this endpoint will be performed asap after data provision by the CRO (expected end 2023) and the Silver nitrate IULCID file under EU REACH will be updated accordingly.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf</p> |         |              |                      |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country        | Organisation   | Type of Organisation    | Comment number |
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| 30.10.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | United Kingdom | <confidential> | Company-Downstream user | 8              |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |                |                         |                |
| <p>Comment on Hazard class as Explosives:</p> <p>Silver nitrate is used in various secondary school science activities and if it is reclassified as an explosive, it will have a huge impact on the curriculum. With over 60 years of experience in supporting secondary schools in health and safety in science and DT activities, we have never received a report of a silver nitrate explosion. We are aware that silver nitrate can explode, however this will only occur when mixed with other chemicals and not on its own. We have a range of guidance that schools can use to implement the necessary control measures when silver nitrate is used in unstable silver nitrate mixtures. In conclusion, we believe that silver nitrate as pure substance should not be classified as an explosive.</p> <p>Comment on Hazard class as Substances which in contact with water emit flammable gases:</p> <p>Silver nitrate is used in various secondary school science activities as water-based solution and if it is reclassified as 'Substances which in contact with water emit flammable gases' it will have a huge impact on the curriculum. With over 60 years of experience in supporting secondary schools in health and safety in science and DT activities, we have never received a report of a silver nitrate emitting flammable gases. We have a range of guidance that schools can use to implement the necessary control measures when preparing and using silver nitrate solutions. In conclusion, we believe that silver nitrate as pure substance should not be classified under Substances which in contact with water emit flammable gases.</p> |                |                |                         |                |

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## HEALTH HAZARDS – Acute toxicity

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 9              |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Country | Organisation | Type of Organisation | Comment number |
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| 09.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Germany |              | MemberState          | 10             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |              |                      |                |
| <p>It is generally agreed that no further testing should be performed and it cannot be performed for CLH purposes in any case. Therefore, thorough analysis of available data is needed.</p> <p>Oral:</p> <p>It is stated in the CLH report that most data on acute oral toxicity could not be traced back to specific publications. However, in the PubChem database (pubchem.ncbi.nlm.nih.gov) an oral LD50 for mice is reported and referenced with PMID: 15408635. In this publication from 1950, silver nitrate was applied to four mice (with a body weight of 20 g) per dose as an aqueous solution via oral gavage and the toxicity range was determined in approximately 40 mice (suggesting ~10 doses) with an observation period of 14 days. The following values are reported: LD0 = 30 mg/kg, LD50 = 50 mg/kg, and LD100 = 65 mg/kg, suggesting a rather steep dose-response curve.</p> <p>In this same database, the human LDLo (lowest known lethal dose) is listed as 29 mg/kg, but it is stated that the route is unreported. Reference is made to a textbook from 1970 (Arena, J.M. "Poisoning: Toxicology, Symptoms, Treatments", 2nd ed, publisher: C.C. Thomas, Springfield, ILL). The BfR accessed the 3rd edition of the book through the Internet Archive (archive.org). However, the chapter on silver salts (p. 430 in the 3rd edition) does not contain the value of 29 mg/kg bw. It is stated there that silver nitrate caustic pencils may be broken and pieces could be ingested by children. Followed by: "Less than 2.5 gm is generally harmless – but larger amounts may cause severe symptoms. Ingestions of between 2.5 and 10 gm may be fatal, and over 10 gm almost always causes death." Considering this and using a conservative approach, 2.5 g ingested by a 70 kg person would amount to an LDLo of 35.7 mg/kg bw. Thus, the value of 29 mg/kg could not be traced back to any source. On the other hand, 10 g is stated to be fatal for humans by other sources (e.g. WHO, possibly also referring back to the Arena textbook) and is cited in the CLH report (i.e. 142.9 mg/kg for a 70 kg person to be viewed as an LD100). Considering such LDLo and LD100 values, an LD50 of 50 mg/kg bw can be considered to also reflect acute oral toxicity of silver nitrate in humans.</p> <p>In the view of the BfR, the mouse value is best supported by a reference and would be the lowest value for the most sensitive species, considering the other LD50 values for silver nitrate reported for mice, guinea pigs, and rats in the CLH report of 129, 473, and 1173 mg/kg bw, respectively. These values are also listed in the PubChem entry along with other values, e.g. oral LDLo values of 800 mg/kg bw and 20 mg/kg bw, for rabbits and dogs, respectively (these values could however not be verified because the source textbook from 1935 was unavailable to the BfR).</p> |         |              |                      |                |

In conclusion, the mouse value (LD50 of 50 mg/kg bw) should be used as ATE. This would still support classification of silver nitrate as Acute Tox. 2, H300.  
Please also note that in the table on p. 45 of the CLH report, 28.6 mg/kg bw is referred to as the LD100 in humans, when in fact it should be considered the LDLo.

**Dermal:**

No classification because of inconclusive data is supported.

**Inhalation:**

No classification because of inconclusive data is supported. Additional labelling with EUH071 is warranted based on the presented data for workers and the skin corrosive properties of silver nitrate and is therefore supported.

| Date                                                                                                                                                                                                                                                                                      | Country | Organisation                        | Type of Organisation          | Comment number |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                | Belgium | European Biocidal Silver Task Force | Industry or trade association | 11             |
| Comment received                                                                                                                                                                                                                                                                          |         |                                     |                               |                |
| Section 10.1 (Acute Toxicity – Oral Route) – The attached document (page 3) explains that data are of insufficient quality to conclude this level of classification with certainty and as such no classification should be proposed for silver nitrate on the basis of insufficient data. |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silver nitrate CLH STF comments - 10 November.pdf                                                                                                                                              |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                       | Country | Organisation | Type of Organisation | Comment number |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                 | Belgium | Umicore      | Company-Importer     | 12             |
| Comment received                                                                                                                                                                                                                                                                                                           |         |              |                      |                |
| Acute toxicity – oral: based on the existing experimental subacute test data with silver nitrate, subacute to subchronic test data with silver acetate and acute toxicity data with other silver compounds (including a soluble silver compound), silver nitrate should not be classified for Acute toxicity – oral route. |         |              |                      |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf                                                                                                                                                          |         |              |                      |                |

**HEALTH HAZARDS – Skin corrosion/irritation**

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 13             |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 09.11.2023 | Germany |              | MemberState          | 14             |



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| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |  |
| Skin Corr. 1A classification is supported based on the data from an OECD TG 431 study from the registration dossier. The 3-minute reading already fulfils criteria for steps 1 and 2 of the prediction model for the epiCS RHE according to the TG (i.e. viability below 50% after 3 minutes for corrosive and viability below 15% after 3 minutes for optional Cat. 1A). This is further supported by the EpiDerm data which, although lacking the 3-minute reading, show cell viability below 15 % at the 60-minute reading. |  |  |  |  |

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 10.11.2023 | Belgium | Umicore      | Company-Importer     | 15             |

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| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |  |  |
| <p>Reliable in vitro studies are available for skin irritation/corrosion potential of silver nitrate. Based on these studies, silver nitrate is corrosive to the skin and a self-classification as Skin Corr. 1A (H314) is included under EU REACH. However, it is recognised that the peer reviewed publications do not provide details on the silver nitrate test items (like particle size). It is suggested that particle size might play a role in the corrosion hazard potential. Therefore, the EPMF is currently performing additional in vitro testing (OECD 435 and 431, GLP compliant) with silver nitrate in three distinct particle sizes. Based on this experimental data (expected towards end 2023), a re-assessment of the skin corrosion potential of silver nitrate will be performed to verify if a Skin corr 1A (self-classification under EU REACH) or 1B classification (existing harmonised classification in CLP Annex VI) is most appropriate. This assessment will be performed asap after data provision by the CRO and the Silver nitrate IULCID file under EU REACH will be updated accordingly.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf</p> |  |  |  |  |

#### **HEALTH HAZARDS – Serious eye damage/eye irritation**

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 09.11.2023 | Germany |              | MemberState          | 16             |

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| Comment received                                                                                                                                                                                                                                                                                                                                                                |  |  |  |  |
| As is correctly stated in the CLH report, Eye Dam. 1 classification is implicated by the proposed Skin Corr. 1A classification and supported by the rabbit data. Therefore, Eye Dam. 1 should have been listed in the proposed and resulting classification tables but without hazard statement code H318 in the labelling column, because this is covered by the text of H314. |  |  |  |  |

#### **HEALTH HAZARDS – Respiratory sensitisation**

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 09.11.2023 | Germany |              | MemberState          | 17             |

|                                                              |  |  |  |  |
|--------------------------------------------------------------|--|--|--|--|
| Comment received                                             |  |  |  |  |
| Because of inconclusive data no classification is supported. |  |  |  |  |

#### **HEALTH HAZARDS – Skin sensitisation**

| Date       | Country | Organisation                        | Type of Organisation          | Comment number |
|------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023 | Belgium | European Precious Metals Federation | Industry or trade association | 18             |

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| More details on this endpoint are provided in the attached document.                                                                    |  |  |  |  |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |  |  |  |  |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country | Organisation | Type of Organisation | Comment number |
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| 09.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Germany |              | MemberState          | 19             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |              |                      |                |
| <p>The proposed classification as Skin Sens. 1, H317 is supported. We have found some additional publications on silver nitrate allergic contact dermatitis that have not been considered in the CLH report. The first case report is of a 42-year-old male who underwent patch testing and reacted to the marking fluid, which contains silver nitrate. Subsequent testing with the ingredients of the marking fluid confirmed sensitisation to silver nitrate (+ + reaction to 1 % in pet. on D4) (DOI 10.1111/j.1600-0536.2009.01566.x). Another case report describes a clearly positive reaction to 1 % silver nitrate in water in a confirmatory patch test after a first patch test induced skin reactions described as “edge effect” from unevenly distributed patch test solution (DOI: 10.1016/S1046-199X(98)90150-6). Positive patch test reactions to silver nitrate were also reported in a study on patients with chronic leg ulcers (n = 75) and a control group without ulcers (n = 82). In this study, 12 % of patients with chronic leg ulcers and 3.6 % of control patients reacted positively to 5 % aqueous silver nitrate solution. When a lower concentration of 1 % was used for patch testing, 6.7 % of patients with leg ulcers and 1.2 % of controls showed positive reactions. Authors concluded that the higher rate of sensitisation in patients with leg ulcers was because of the management of the ulcers with topical drugs containing silver nitrate (DOI: doi/10.1111/j.1600-0536.2007.01253.x).</p> |         |              |                      |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                               | Country | Organisation                        | Type of Organisation          | Comment number |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                         | Belgium | European Biocidal Silver Task Force | Industry or trade association | 20             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                   |         |                                     |                               |                |
| <p>Section 10.7 (Skin Sensitisation) – The attachment document (pages 3-4) explains that, to be consistent with the CLH decision for silver metal and silver zinc zeolite, silver nitrate should not be classified for skin sensitisation.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silver nitrate CLH STF comments - 10 November.pdf</p> |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                | Country | Organisation | Type of Organisation | Comment number |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                          | Belgium | Umicore      | Company-Importer     | 21             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                    |         |              |                      |                |
| <p>The present CLH report refers to the same dataset than the one provided to and discussed by the RAC for silver metal and silver zinc zeolite, and should also be void of a classification of silver nitrate for skin sensitisation.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf</p> |         |              |                      |                |

#### HEALTH HAZARDS – Germ cell mutagenicity

| Date | Country | Organisation | Type of Organisation | Comment |
|------|---------|--------------|----------------------|---------|
|------|---------|--------------|----------------------|---------|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |                        |                      | number |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------|----------------------|--------|
| 09.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Netherlands | Ishizuka Glass Co. Ltd | Company-Manufacturer | 22     |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                        |                      |        |
| <p>The data submitted to propose classification for silver nitrate for germ cell mutation (Category 2) is largely the same data that were submitted to propose classification for silver (CAS No. 7440-22-4). The new data submitted for silver nitrate are limited to 9 published articles describing in vitro studies. These studies are old, poorly reported and not conducted to GLP or any test guideline. The results are negative for effects with bacteria (6 studies) which, as has been noted by RAC, are influenced by the bactericidal properties of silver and are therefore of limited value. The conclusions regarding positive effects in the 3 remaining studies are overstated given the incomplete nature of the data and the fact that the results of the in-vitro data with silver complexes (SCAS), to which they are linked by the DS, are not universally positive but instead show a mix of positive/negative and equivocal results. The mutagenicity data submitted in the CLH dossiers for both silver nitrate and silver consist of 13 studies conducted in vitro with silver complexes (SCAS) and 6 studies conducted in vivo with the same SCAS and 3 studies conducted in vivo with nanosilver. Based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 46), the in vitro dataset for silver nitrate can be regarded in the same way as silver, being “sparse and incomplete for ionic (soluble) salts and Ag+-releasing SCAS and they are more ideally considered to supplement the data for silver and be weighed on a case-by-case basis as such”.</p> <p>Based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 52), the in vivo dataset for silver nitrate, although reliable, can in the same way as silver be considered lacking, because “SCAS such as zeolites and other ion exchangers may not be relevant because they release only small amounts of silver ion that cannot be properly tested and are likely to give a negative result because insufficient silver ions are available to the testing environment”.</p> <p>The overall conclusion for the classification of silver nitrate for mutagenicity can be based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 54) which states that “while the mutagenicity database for silver is extensive for several forms and compounds of silver, the data are inconclusive overall because of contradictory findings and in many cases a lack of sufficient information for each study report. Some concerns remain with respect to the in vivo findings for both chromosomal aberrations and DNA strand breaks but the negative results generally in this case outweigh the positive ones”. Accordingly, and to be consistent with the CLH decision for silver, the classification recommendation for silver nitrate should be no classification for mutagenicity due to inconclusive data.</p> <p>More specific comments on comparison with the CLP criteria are included in Appendix 1 of the attached document..</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment 231108_RAC_Public Consultation Silver nitrate_comments Ishizuka.pdf</p> |             |                        |                      |        |

| Date                                                                                                                                                                                                                                | Country | Organisation             | Type of Organisation | Comment number |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------------------|----------------------|----------------|
| 09.11.2023                                                                                                                                                                                                                          | Poland  | LANXESS Deutschland GmbH | Company-Manufacturer | 23             |
| Comment received                                                                                                                                                                                                                    |         |                          |                      |                |
| <p>Silver nitrate classification for mutagenicity is not supported by conclusive data. Please refer to LANXESS position paper, attached.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public</p> |         |                          |                      |                |

attachment LANXESS position paper on proposal for classification of silver nitrate final.pdf

| Date                                                                                                                                                                                                                                                                                                                                                                                   | Country | Organisation | Type of Organisation | Comment number |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 09.11.2023                                                                                                                                                                                                                                                                                                                                                                             | Germany |              | MemberState          | 24             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                       |         |              |                      |                |
| The DE-CA supports the proposal for Muta. 2 classification. Based on the available data, it is not possible to fully exclude a genotoxic potential for silver ions. In light of several negative results and shortcomings of the positive studies, as well as uncertainties because of the read-across approach, evidence is not convincing enough to place silver nitrate in Cat. 1B. |         |              |                      |                |

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 25             |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Country | Organisation   | Type of Organisation | Comment number |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------|----------------------|----------------|
| 30.10.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Germany | <confidential> | Company-Manufacturer | 26             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                |                      |                |
| <p>The data presented for the proposal to classify silver nitrate (CAS No. 7761-88-8) as Muta. 2 are largely consistent with the data presented for the proposal to classify silver (CAS No. 7440-22-4). The new data submitted for silver nitrate are limited to nine published articles describing in vitro studies. These studies are old, inadequately reported and were not conducted according to GLP or other testing guidelines.</p> <p>Based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 46), the in vitro dataset for silver nitrate can be regarded in the same way as silver, being “sparse and incomplete for ionic (soluble) salts and Ag+-releasing SCAS and they are more ideally considered to supplement the data for silver and be weighed on a case-by-case basis as such”.</p> <p>Based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 52), the in vivo dataset for silver nitrate, although reliable, can in the same way as silver be considered lacking, because “SCAS such as zeolites and other ion exchangers may not be relevant because they release only small amounts of silver ion that cannot be properly tested and are likely to give a negative result because insufficient silver ions are available to the testing environment”.</p> <p>The overall conclusion for the classification of silver nitrate for mutagenicity can be based on the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 54) which states that “while the mutagenicity database for silver is extensive for several forms and compounds of silver, the data are inconclusive overall because of contradictory findings and in many cases a lack of sufficient information for each study report. Some concerns remain with respect to the in vivo findings for both chromosomal aberrations and DNA strand breaks but the negative results generally in this case outweigh the positive ones”. Accordingly, and to be consistent with the CLH decision for silver, the classification recommendation for silver nitrate should be no classification for mutagenicity due to inconclusive data.</p> |         |                |                      |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Country | Organisation                        | Type of Organisation          | Comment number |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Belgium | European Biocidal Silver Task Force | Industry or trade association | 27             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |                                     |                               |                |
| <p>Section 10.8 (Classification for germ cell mutation) – The attached document (page 4) explains that the overall conclusion for the classification of silver nitrate for mutagenicity can be based on the RAC opinion for silver. The attached document (pages 4-9) also includes specific comments comparing the Dossier Submitter's report with the CLP criteria. The conclusion of that assessment is that data with AgNPs are inappropriate, leaving insufficient data to address the potential for gene mutation in vivo with silver nitrate. Accordingly, for this reason, and to be consistent with the CLH decision for silver, the classification recommendation for silver nitrate should be no classification for mutagenicity due to inconclusive data.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silver nitrate CLH STF comments - 10 November.pdf</p> |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country | Organisation | Type of Organisation | Comment number |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Belgium | Umicore      | Company-Importer     | 28             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |              |                      |                |
| <p>The present CLH report refers to roughly the same dataset than the one provided to and discussed by the RAC for silver metal. In line with the presented read-across approach for silver nitrate, and by considering today's available relevant and reliable data, silver nitrate should be void of a classification for germ cell mutagenicity. It is recognised that the positive signal in a mammalian cell gene mutation assay requires further investigation in order to clarify the potential for simple ionic silver substances to induce point mutation in mammalian cells. However, the performance of a follow-up in vivo assay is postponed until the outcome of the ongoing 2-year carcinogenicity assay is known (cfr. next point), in line with the EU REACH requirements.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf</p> |         |              |                      |                |

### HEALTH HAZARDS – Carcinogenicity

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Country | Organisation | Type of Organisation | Comment number |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 10.11.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Belgium | Umicore      | Company-Importer     | 29             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |              |                      |                |
| <p>There is an ongoing OECD453 and GLP compliant study with silver acetate (Charles River Den Bosch, NL). The in-life phase will be terminated in November-December 2023 and a draft report is expected mid-2024. This study will inform about the carcinogenic potential of silver acetate and, via read-across, also silver nitrate.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf</p> |         |              |                      |                |

| Date             | Country | Organisation | Type of Organisation | Comment number |
|------------------|---------|--------------|----------------------|----------------|
| 09.11.2023       | Germany |              | MemberState          | 30             |
| Comment received |         |              |                      |                |

Because of inconclusive data no classification is supported, considering the previous RAC analysis of available data with silver zinc zeolite and the absence of data with silver nitrate.

#### HEALTH HAZARDS – Reproductive toxicity

| Date       | Country     | Organisation           | Type of Organisation | Comment number |
|------------|-------------|------------------------|----------------------|----------------|
| 09.11.2023 | Netherlands | Ishizuka Glass Co. Ltd | Company-Manufacturer | 31             |

#### Comment received

There are no substance specific data on the reproductive effects of silver nitrate. In the absence of data, existing studies conducted mostly with silver acetate have been used in a read-across approach by the DS in order to conclude classification for silver nitrate. The assumption in this approach is that the observed reproductive toxicity is derived from the silver ion.

According to the ECHA Guidance on Grouping of Chemicals (Chapter R.6) the effect of the counter ion should also be taken into account for read across between metal compounds. This is particularly important in the case of silver nitrate as there are fundamental toxicological differences between silver acetate and silver nitrate.

In various parts of the CLH dossier the bioavailability of silver (ion) from silver acetate and silver nitrate is described as being similar, with an implication that effects observed with silver acetate can therefore be read across directly to silver nitrate for classification. The evidence given for similarity is the comparative toxicokinetic study (Anonymous et al – 2021) submitted in Section 9. It is important to note that in this study silver acetate and silver nitrate were administered via gavage and therefore directly introduced into the gastric fluid. In this situation, silver acetate and silver nitrate will both be rapidly converted to the same chloride/chloride complexes, so in this case it is unsurprising that silver (ion) bioavailability is similar.

Data measuring the effects of dosing silver nitrate directly to test animals are lacking. The 28 day RDT study IIIA 6.3.1-07 is cited as indicating systemic doses up to 100 mg silver nitrate/kg bw/d are well-tolerated by rats, but this study has the same limitation created by gavage dosing as described above. Direct acute or corrosive/irritation effects are by-passed by gavage application, so it remains unknown whether the reproductive toxicity data developed using dietary administration of silver acetate are directly applicable to silver nitrate in a read-across framework. The study by Matuk (IIIA 6.5-03) contains some evidence of significant toxicity (rapid weight loss from week 23 onwards and eventually death) following administration at 222 mg/kg bw via drinking water, but without comparable silver acetate data the influence of nitrate compared to acetate is unknown. According to the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 83), “the data available on silver acetate and nanosilver indicate that the silver ion can cause adverse effects on sexual function and fertility possibly by a mechanism involving oxidative stress and perturbations of Cu homeostasis. However, a classification of 1B is dependent on having sufficiently robust data to support the proposal”.

In the case of silver nitrate, although the mechanism of toxicity via silver ion exposure is plausible, experimental data are lacking to determine the influence of nitrate on general toxicity (acute effects and local corrosivity) and whether or not this would exacerbate effects seen with silver acetate to the point where the animals would suffer more marked general toxicity that would preclude classification.

Substances are classified in Category 2 if there is “some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1.”

Since evidence of the contribution to toxicity from the nitrate anion is absent this should present sufficient concern for uncertainty. Classifying silver nitrate in Category 1B based

solely on extrapolating silver ion exposure from silver acetate should not be warranted for effects on sexual function and fertility, and effects on development. The concerns linked to effects resulting from the silver ion are adequately addressed with Category 2 according to the above criteria, with classification at this level then consistent with the existing RAC opinions for metallic silver and silver zinc zeolite which are based largely on the same data supporting the current proposal.

More specific comments on comparison with the CLP criteria are included in Appendix 2 of the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 231108\_RAC\_Public Consultation Silver nitrate\_comments Ishizuka.pdf

| Date       | Country | Organisation                | Type of Organisation | Comment number |
|------------|---------|-----------------------------|----------------------|----------------|
| 09.11.2023 | Poland  | LANXESS<br>Deutschland GmbH | Company-Manufacturer | 32             |

#### Comment received

Concerns related to the effects of the silver ion are adequately addressed by Reproductive toxicity Category 2.

Please refer to LANXESS position paper, attached.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment LANXESS position paper on proposal for classification of silver nitrate final.pdf

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 09.11.2023 | Germany |              | MemberState          | 33             |

#### Comment received

The proposed classification as Repr. 1B, H360FD is supported primarily based on results obtained in the EOGRTS using silver acetate.

While the available studies provide clear evidence for a developmental toxicity of silver nitrate, consequently resulting in a classification in category 1, the data appear less conclusive with respect to adverse effects sexual function and fertility:

In the absence of studies conducted with silver nitrate, the EOGRTS using silver acetate appears to be the most reliable source for drawing conclusions regarding possible fertility effects of silver nitrate. In the study in question, statistically significant effects on sperm parameters (including reduced testicular and cauda epididymal total spermatid and sperm counts) occurred in F1 males, demonstrating an adverse effect of silver ions on fertility. In contrast, the sperm parameters obtained in P0 males are less suitable to provide sufficient evidence for a similar adverse effect also in these animals:

Statistical significance is only shown by reduced testis weight and spermatid count total (million), whereby the latter parameter is not subject to a plausible dose-response relationship. The effect on testis weight is relatively weak and all sperm motion and sperm morphology values are unaffected, also the fertility indices (m) are undisturbed. Thus, with regard to effects on sperm, the study in question suggests primarily a risk to animals exposed during their development, so that the question may arise whether the sperm effects observed in F1 are to be interpreted primarily as adverse effects on sexual function and fertility or as developmental toxicity.

With regard to the other studies available, there are also doubts as to whether they are suitable for indicating fertility effects in F0 males with a degree of certainty that would permit classification in category 1:

- The studies performed with silver nanoparticles are for the most part of substandard



quality, suffer from low data depth or unclear relevance. In the RAC opinion on silver, these studies were assessed as indicative of a category 2 classification.

- The second study with silver acetate, evaluated by the dossier submitter as evidence of a category 1 classification, has various deficiencies such as missing single animal data, missing histopathological examination of reproductive organs, and missing statistics. Moreover, it is remarkable that the stomach weight of the parental females decreased drastically (-40 %) under treatment with silver acetate, which, in view of the known effect of silver ions on mucous membranes, raises the question of whether excessive maternal toxicity was present.

Relevance of adverse effects on sexual function and fertility for classification is defined according to the Guidance on the Application of the CLP Criteria as:

“clear evidence of an adverse effect on sexual function and fertility [...] [and] if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects.”

In order to assess whether a marked general toxicity was present in the EOGRTS with silver acetate, the dossier submitter relies primarily on the body weight gain of the treated animals. At this point, it would be helpful if the partly drastic effects of treatment on serum copper and selenium levels (up to -88%) were placed in a broader context with the issue of nonspecific toxicity.

However, since the CLP Guidance significantly constrains the relationship between parenteral toxicity and adverse fertility effects compared to the relationship to developmental toxic effects, it is comprehensible why the fertility effects observed in the EOGRTS are considered to be fully relevant to classification (CLP Guidance: “There is no established relationship between fertility effects and less marked systemic toxicity.

Therefore, it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity.”).

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 34             |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Country | Organisation   | Type of Organisation | Comment number |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------|----------------------|----------------|
| 30.10.2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Germany | <confidential> | Company-Manufacturer | 35             |
| Comment received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                |                      |                |
| There are no substance specific data on the reproductive effects of silver nitrate. In the absence of data, existing studies conducted mostly with silver acetate have been used in a read-across approach in order to conclude classification for silver nitrate. The assumption in this approach is that the observed reproductive toxicity is derived from the silver ion. According to the ECHA Guidance on Grouping of Chemicals (Chapter R.6) the effect of the counter ion should also be taken into account for read across between metal compounds. This is particularly important in the case of silver nitrate as there are fundamental toxicological differences between silver acetate and silver nitrate. According to the RAC opinion for silver (CLH-O-0000007152-82-01/F, Page 83), “the data available on silver acetate and nanosilver indicate that the silver ion can cause adverse |         |                |                      |                |

effects on sexual function and fertility possibly by a mechanism involving oxidative stress and perturbations of Cu homeostasis. However, a classification of 1B is dependent on having sufficiently robust data to support the proposal”.

In the case of silver nitrate, although the mechanism of toxicity via silver ion exposure is plausible, experimental data are lacking to determine the influence of nitrate on general toxicity (acute effects and local corrosivity).

Substances are classified in Category 2 if there is “some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1.”

In the absence of evidence on the contribution of the nitrate anion to toxicity, this should present sufficient concern for uncertainty. The classification of silver nitrate in category 1B, based solely on the extrapolation of silver ion exposure from silver acetate, should not be justified for effects on sexual function and fertility and on development. The concerns related to the effects of silver ion are adequately addressed by the classification in category 2 according to the above criteria, and the classification at this level then consistent with the existing RAC opinions on metallic silver and silver-zinc zeolite, which are largely based on the same data supporting the current proposal.

| Date       | Country | Organisation                        | Type of Organisation          | Comment number |
|------------|---------|-------------------------------------|-------------------------------|----------------|
| 10.11.2023 | Belgium | European Biocidal Silver Task Force | Industry or trade association | 36             |

#### Comment received

Section 10.10 (Reproductive toxicity) – The attached document (pages 9-17) explains why classifying silver nitrate in Category 1B, based solely on extrapolating silver ion exposure from silver acetate, is not warranted for effects on sexual function and fertility, and effects on development. Instead, the concerns linked to effects resulting from the silver ion are adequately addressed with Category 2 according to the CLP criteria. Classification at this level is consistent with the existing RAC opinions for metallic silver and silver zinc zeolite which are based largely on the same data supporting the current proposal.

Section 10.10.1-3 (Effects on sexual function and fertility) – The attached document (pages 10-14) provides detailed comments comparing the Dossier Submitter's report with the CLP criteria.

Section 10.10.4-6 (Adverse effects on development) – The attached document (pages 14-17) provides detailed comments comparing the Dossier Submitter's report with the CLP criteria.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Silver nitrate CLH STF comments - 10 November.pdf

| Date       | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 10.11.2023 | Belgium | Umicore      | Company-Importer     | 37             |

#### Comment received

The present CLH report refers to roughly the same dataset than the one provided to and discussed by the RAC for silver metal. In line with the presented read-across approach for silver nitrate, and by considering today's available relevant and reliable data, silver nitrate is self-classified as Reproductive Toxicant 1B (H360D) following the identification of developmental toxicity in an EOGRTS with silver nitrate. For reproductive performance and fertility, the available evidence does however not support a classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf

#### **HEALTH HAZARDS – Specific target organ toxicity - single exposure**

| Date                                                                                                                                                    | Country | Organisation | Type of Organisation | Comment number |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 09.11.2023                                                                                                                                              | Germany |              | MemberState          | 38             |
| Comment received                                                                                                                                        |         |              |                      |                |
| No classification for STOT SE is supported based on other proposed classifications that cover effects observed after single exposure to silver nitrate. |         |              |                      |                |

#### **HEALTH HAZARDS – Specific target organ toxicity - repeated exposure**

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 39             |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                                                                                                                                                                                                              | Country | Organisation | Type of Organisation | Comment number |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 09.11.2023                                                                                                                                                                                                                                                                                                                                        | Germany |              | MemberState          | 40             |
| Comment received                                                                                                                                                                                                                                                                                                                                  |         |              |                      |                |
| The proposed classification of silver nitrate as STOT RE 2 (nervous system) is supported based on the effects observed on brain histopathology and neurotransmitters as well as developmental neurotoxic effects. It should be analysed if data are sufficient to conclude on the absence of such effects after inhalational and dermal exposure. |         |              |                      |                |

| Date                                                                                                                                                                        | Country | Organisation | Type of Organisation | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|--------------|----------------------|----------------|
| 10.11.2023                                                                                                                                                                  | Belgium | Umicore      | Company-Importer     | 41             |
| Comment received                                                                                                                                                            |         |              |                      |                |
| Using relevant and reliable repeated dose toxicity studies with silver nitrate and read-across substances (like silver acetate), a STOT RE classification is not supported. |         |              |                      |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment Umicore - final comments - Silver nitrate CLH public consultation .pdf           |         |              |                      |                |

#### **ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment**

| Date                                                                                   | Country        | Organisation                | Type of Organisation | Comment number |
|----------------------------------------------------------------------------------------|----------------|-----------------------------|----------------------|----------------|
| 09.11.2023                                                                             | United Kingdom | Health and Safety Executive | National Authority   | 42             |
| Comment received                                                                       |                |                             |                      |                |
| Silver nitrate (EC: 231-853-9; CAS: 7761-88-8)                                         |                |                             |                      |                |
| The chronic aquatic toxicity Table (2) in the CLH report (page 307) includes a Daphnia |                |                             |                      |                |

magna 21-day endpoint of 0.0011 mg/L (mean measured dissolved silver recalculated to AgNO<sub>3</sub>) for the study by Nebeker (1983). It is unclear from the table whether this endpoint is a NOEC or EC<sub>10</sub> value and it does not appear to match the text that states the “value” for survival and reproduction from this study is 0.0019 mg/L. The 0.0019 mg/L value appears to be a typo as the NOEC based on measured dissolved silver is 0.0007 mg/L which recalculated to AgNO<sub>3</sub> is 0.00109 mg/L (rounded up to 0.0011 mg/L). Based on comparison with Annex 1 of the CLH report on silver (ECHA, 2020), we note this 0.0011 mg/L value is a reproduction NOEC rather than EC<sub>10</sub>. Please could the CLH DS clarify this?

ECHA (2020) CLH report (including Annexes): Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Silver; Date: September 2020.

| Date                                                                                                                                    | Country | Organisation                        | Type of Organisation          | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------|-------------------------------|----------------|
| 08.11.2023                                                                                                                              | Belgium | European Precious Metals Federation | Industry or trade association | 43             |
| Comment received                                                                                                                        |         |                                     |                               |                |
| More details on this endpoint are provided in the attached document.                                                                    |         |                                     |                               |                |
| ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH Silver nitrate_EPMFcmts_final_231107.pdf |         |                                     |                               |                |

| Date                                                                                                                                                            | Country     | Organisation | Type of Organisation | Comment number |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|----------------------|----------------|
| 31.10.2023                                                                                                                                                      | Netherlands |              | MemberState          | 44             |
| Comment received                                                                                                                                                |             |              |                      |                |
| We agree with the proposed classification noting that the same acute and chronic ERVs are used as for silver (powder and nano) and converted to silver nitrate. |             |              |                      |                |

#### PUBLIC ATTACHMENTS

1. Silver nitrate CLH STF comments - 10 November.pdf [Please refer to comment No. 4, 11, 20, 27, 36]
2. Umicore - final comments - Silver nitrate CLH public consultation .pdf [Please refer to comment No. 5, 7, 12, 15, 21, 28, 29, 37, 41]
3. 231108\_RAC\_Public Consultation Silver nitrate\_comments Ishizuka.pdf [Please refer to comment No. 22, 31]
4. LANXESS position paper on proposal for classification of silver nitrate final.pdf [Please refer to comment No. 23, 32]
5. CLH Silver nitrate\_EPMFcmts\_final\_231107.pdf [Please refer to comment No. 2, 6, 9, 13, 18, 25, 34, 39, 43]