Scientific Committee on Consumer Safety

SCCS

OPINION on
Silver Zinc Zeolite
(CAS No. 130328-20- 0, EC No. 603-404-0)

The SCCS adopted this document
by written procedure on 21 December 2023

ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 22 March to 5 June 2023). Comments received during this period were considered by the SCCS. For this Opinion, main changes occurred in the SCCS comment in the inhalation exposure, and the MoS was adapted accordingly.

All Declarations of Working Group members are available on the following webpage:
Register of Commission expert groups and other similar entities (europa.eu)

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the classification as Toxic for reproduction Cat. 2, does the SCCS consider Silver Zinc Zeolite safe when used as a preservative in cosmetic products according to the specifications and concentration limits provided in the dossier submission?*

   The SCCS considers that Silver Zinc Zeolite (CAS No. 130328-20-0) incorporating a maximum silver content of 2.5% is safe in spray deodorant and powder foundation when used at the proposed concentration of 1%.

2. *Alternatively, what is, according to the SCCS, the maximum concentration considered safe for use of Silver Zinc Zeolite as a preservative in cosmetic products?*

   /

3. *Does the SCCS have any further scientific concerns with regard to the use of Silver Zinc Zeolite in cosmetic products?*

   /

Keywords: SCCS, scientific opinion, silver zinc zeolite, Regulation 1223/2009, CAS No. 130328-20- 0, EC No. 603-404-0.

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These Committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), and they are made up of scientists appointed in their personal capacity.

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SCCS
The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Silver Zinc Zeolite (SZZ) (CAS No. 130328-20-0, EC No. 603-404-0) with INCI name 'Ammonium Silver Zinc Aluminium Silicate' is included in the European database for information on cosmetic substances and ingredients (CosIng) with the reported functions of 'absorbent', 'deodorant' and 'preservative'.

SZZ is used for the antimicrobial effects exerted by the silver ions released. Silver ions may interact with the cell membrane of microorganisms and the electron transport processes, bind to nucleic acids, inhibit enzymes and catalyse the formation of free radical oxygen species (ROS). Generally, the antimicrobial effect dependents on how much of the silver is released.

In December 2015, the Risk Assessment Committee (RAC) of ECHA issued an Opinion[1] recommending a 'Toxic for reproduction Category 2' classification (*i.e*. suspected of damaging the unborn) for Silver Zinc Zeolite.
In May 2017, the Commission Regulation No. 2017/776[2] amended - for the purposes of its adaptation to technical and scientific progress - Regulation No. 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (CLP Regulation). In particular, a new entry in Annex VI to the CLP Regulation was added for '*Silver Zinc Zeolite (Zeolite, LTA framework type, surface-modified with silver and zinc ions) [This entry covers LTA (Linde Type A) framework type zeolite which has been surface-modified with both silver and zinc ions at contents Ag+ 0,5 %-6 %, Zn2 + 5 %-16 %, and potentially with phosphorus, NH4+, Mg2+ and/or Ca2+ each at level < 3 %]*'.
In May 2019, the Commission Regulation No. 2019/831 amended Annexes II, III and V to Regulation (EC) No. 1223/2009 (Cosmetics Regulation) following the provisions of Article 15 on CMR substances and the substance Silver Zinc Zeolite was added in entry 1597 of Annex II as a prohibited substance in cosmetic products.
In August 2020, the Commission services received a dossier submission by industry to support the safety assessment of SZZ as a preservative in cosmetic products, in particular in spray deodorant and powder foundation. A positive outcome of this assessment may support the de-listing of SZZ from Annex II and its inclusion under Annex V to the Cosmetics Regulation as an authorised preservative.
In March 2021, the Biocidal Products Committee (BPC) published their Opinion[3] on the application for approval of the active substance Silver Zinc Zeolite. The overall conclusion of the BPC was that SZZ in product type (PT) 4 may not be approved. More specifically, according to the Committee the criteria laid down in point (b)(iii) of Article 19(1) of Regulation No. 528/2012 were not met. The active substance did not fulfil the criteria according to Article 28(2) to enable inclusion in Annex I of Regulation No. 528/2012. SZZ raised concerns for human health and the environment (Repr. 2, Skin Irrit. 2, Eye Dam. 1 and as Aquatic acute 1).
In light of the information provided, the Commission requests the SCCS to carry out a safety assessment on Silver Zinc Zeolite when used as a preservative in cosmetic products.

[1] https://echa.europa.eu/documents/10162/ce343f0e-623b-7678-586e-613dffbcfe06
[2] https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32017R0776
[3] https://echa.europa.eu/documents/10162/2bc163bb-1653-a756-6923-6546ea99f4b6

Terms of reference

1. *In light of the data provided and taking under consideration the classification as Toxic for reproduction Cat. 2, does the SCCS consider Silver Zinc Zeolite safe when used as a preservative in cosmetic products according to the specifications and concentration limits provided in the dossier submission?*

2. *Alternatively, what is, according to the SCCS, the maximum concentration considered safe for use of Silver Zinc Zeolite as a preservative in cosmetic products?*

3. *Does the SCCS have any further scientific concerns with regard to the use of Silver Zinc Zeolite in cosmetic products?*

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Silver Zinc Zeolite (ammonium silver zinc aluminium silicate).

3.1.1.2 Chemical names

EC name: Zeolites, AgZn.

CAS name: Zeolites, AgZn.

IUPAC name: Silver Zinc Zeolite (Zeolite, LTA framework type, surface-modified with silver and zinc ions). This entry covers LTA framework type zeolite which has been surface-modified with both silver and zinc ions at contents Ag 0.5%-6%, Zn 5%-16%, and potentially with phosphorus oxides, NH^{4+}, Mg^{2+} and/or Ca^{2+} each at levels of <3%.

3.1.1.3 Trade names and abbreviations

The SZZ grades supported in this application are Ceramedic CW and Ceramedic CJ.

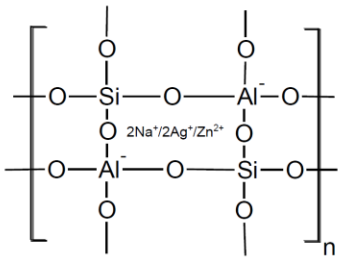
3.1.1.4 CAS / EC number

Cas No: 130328-20-0

EC number: 603-404-0

3.1.1.5 Structural formula

Not applicable. The generic structure of Silver Zinc Zeolite is shown below.



3.1.1.6 Empirical formula

Molecular formula:
Generic form: Ag_2O ZnO (Na_2O Al_2O_3 SiO_2)

3.1.2 Physical form

Property	Value	Reference
State of the substance at 20°C and 101.3 kPa	Solid	-

3.1.3 Molecular weight

Not applicable to the generic definition.

3.1.4 Purity, composition and substance codes

Zeolite, LTA1 framework type, surface-modified with silver and zinc ions, % purity >99 %. The Ceramedic CW/CJ and Zeomic AK/AJ substances are different grades of silver zinc zeolite, as detailed in the table below.

SZZ	**Silver content (wt %)**	**Zinc content (wt %)**	**Water content (wt %)**
Ceramedic CW	0.55	13.5	10 - 20
Ceramedic CJ	2.5	13.5	10 - 20
Zeomic Type AK10D	5.5	14	1-5
Zeomic Type AJ10D	2.5	13.5	1-5

SCCS comment
The analytical methods used for the determination of the exact composition and the purity of the test substance and data on representative batches of the test substance should be provided, according to the SCCS Notes of Guidance.

3.1.5 Impurities / accompanying contaminants

A certificate of analysis of Ceramedic CJ with concentration levels of major elements and heavy metal impurities was confidentially provided to the SCCS: the content of lead was less than 20 ppm and arsenic less than 5 ppm. The concentration of heavy metals present as impurities should be kept as low as possible.

3.1.6 Solubility

Water solubility: SZZ itself is insoluble in water; however, in aqueous environments the substance releases zinc and silver ions.

Taken from CAR-ECHA (2021): Solubility in water (g/l or mg/l, state temperature). For the group of silver zinc zeolites complying with the generic definition: silver zinc zeolite as such is not soluble in water.
With respect to silver and zinc release (based on Bussey 2001 and on Harlan 2010):

- In distilled water pH adjusted with nitric acid or sodium hydroxide (based on a zeolite with 2.5% Ag and 14.4% Zn and a loading of 10 g/l):
    - Silver (max conc.)
        - pH 5: 9.2 mg/l (after 29 days)
        - pH 7: 2.9 mg/l (after 11 days)
        - pH 9: 0.2 mg/l (after 35 days)
    - Zinc (max conc.)
        - pH 5: 467 mg/l (after 37 days)
        - pH 7: 51 mg/l (after 37 days)
        - pH 9: 0.5 mg/l (after 17 days)
- In buffered solutions and a loading of 2 mg/ml (based on a zeolite with 3.8% Ag and 6.6% Zn and a loading of 2 mg/l)
    - Silver (max conc.)
        - pH 5 (phthalate buffer): 23.9 mg/l
        - pH 7 (phosphate buffer): 0.02 mg/l
        - pH 9 (borate buffer): 0.17 mg/l
- Under various conditions using a loading of 50 mg Ag/l (based on zeolites with 2.1% Ag and 5% Ag):
    - Distilled water:
        - max. 0.07 mg Ag/l (0.15% of Ag available), pH: ~9
    - Hard water, pH 6-7, 20°C
        - max. 1.06 mg Ag/l (2.1%)
    - Phosphate buffer at 37 °C (physiological conditions):
        - 8-21 mg Ag/l (16-42%), pH 4
        - 0.5-11 mg Ag/l (0.9-23%), pH 8

Solubility in organic solvents (in g/l or mg/l, state temperature):
For the group of silver zinc zeolites complying with the generic definition: not applicable to an inorganic crystalline solid which is not soluble in water or in organic solvents

SCCS comment
For the calculation of the systemic exposure dose (SED), the applicant proposes a release of silver of 18% for dermal and inhalation exposure and a silver release of 100% in the gastric environment upon ingestion. The SCCS considers these values sufficiently conservative, and will use these for the calculation of the SED.

3.1.7 Partition coefficient (Log Pow)

Measurement or calculation of the partition coefficient is not applicable to an inorganic crystalline complex that is insoluble in water and organic solvents.

3.1.8 Additional physical and chemical specifications

- organoleptic properties (colour, odour, taste if relevant): /
- melting point: no melting point <350°C
- boiling point: not relevant due to the high melting point
- flash point: not applicable
- vapour pressure: the vapour pressure is estimated to be very low ($<10^{-5}$ Pa)
- density: 2.1 (relative density)
- viscosity: not applicable, SZZ as manufactured is a solid with a melting point >40°C
- pKa: not applicable, SZZ does not contain any acid or base functionality
- pH: /
- refractive index: /
- UV/visible light absorption spectrum:/
- Surface tension: not applicable; Silver Zinc Zeolite is insoluble in water

- Flammability: SZZ has no capacity to initiate or support combustion; all components are inorganic and non-pyrophoric. Based on the structure and experience in use, it can be concluded that SZZ is not flammable.
- Granulometry: AK10D* particle size 2.467 ± 1.870 µm, no particles in the nano range. AJ10D** particle size 2.827 ± 2.550 µm, no particles in the nano range. * Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK); ** Zeomic Type AJ10N SZZ (AgION® Silver Antimicrobial Type AJ)

SCCS comment
According to the applicant, their SSZ material does not contain nanoparticles. The CAR-ECHA 2021 report does not state that it could be nano. It also states that, with respect to physicochemical data, only small differences in the results are anticipated among different zeolites as in reality most of the parameters are not relevant due to the nature of the substance.
For granulometry, CAR-ECHA (2021) considers the laser scanning acceptable.

Most of the information provided in the Physicochemical part of the dossier is related to Zeolite, LTA1 framework type, surface-modified with silver and zinc ions Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK) and Zeomic Type AJ10D SZZ (AgION® Silver Antimicrobial Type AJ).

Upon request by the SCCS to provide the exact crystalline structure and particle shape of the two SZZ grades supported in this application (Ceramedic CW and Ceramedic CJ) from appropriate analytical method(s) such as electron microscopy (SEM, TEM, STEM), atomic force microscopy (AFM), Raman spectroscopy, etc., the Applicant has submitted a reference XRD pattern of the crystal structure of a Linde Type A zeolite and data on various batches of Zeolite type AJ.
The SCCS accepts that the material does not consist of nano particles.

Source: International Zeolite Association

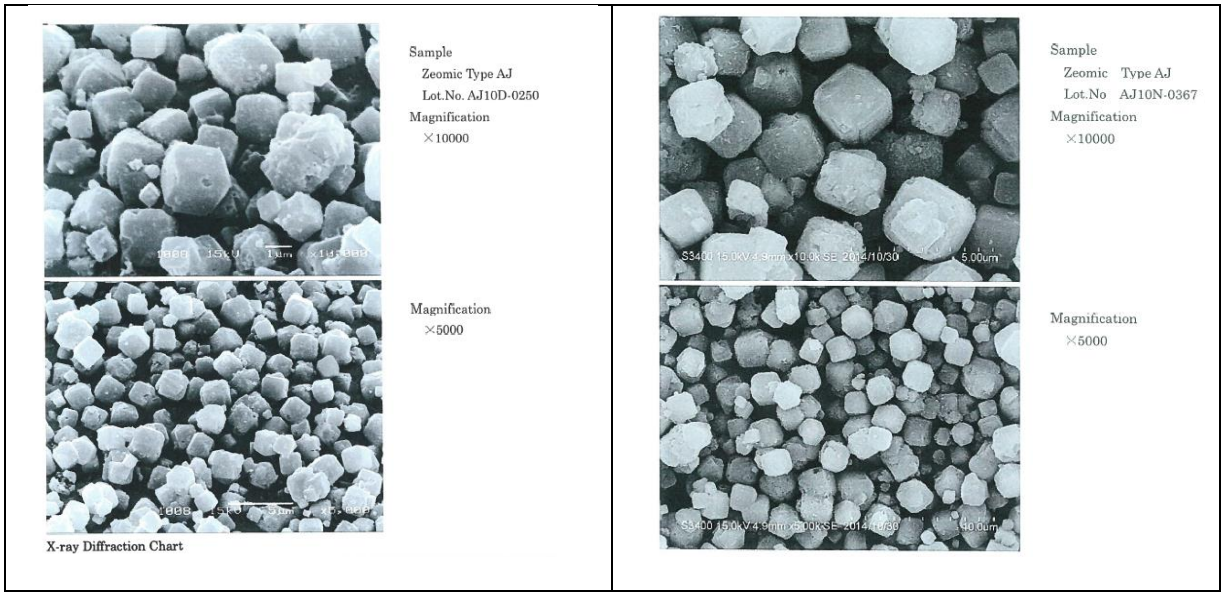


Figure 1. Zeomic AJ Lot AJ10D-0250 (left) and Zeomic AJ Lot AJ10N-0367

Figure 2.

3.1.9 Homogeneity and Stability

According to the Applicant, this inorganic substance is stable with the exception of the intentional release of silver and zinc ions in aqueous media through ion exchange. As explained in 3.1.6 (Solubility), a silver release of 18% from the substance will be used for dermal and inhalation exposure.

SCCS comment
The SCCS received confidential data on the stability of Zeomic® type AJ10D, AJ10N and AJ10H Silver Zeolite A. Based on the results of these stability studies, the major elements of the above-mentioned types of Zeomics were found stable for one year when stored under warehouse conditions and at elevated temperature 40-45 °C without any control of humidity and light.

3.2 TOXICOKINETICS

SSZ
According to the Applicant, Zeolite is chemically and toxicologically inert and will therefore not be absorbed systemically.
According to CAR-ECHA (2021), the substance-specific toxicokinetic information is limited to a study investigating dermal absorption or subcutaneously administered silver zinc zeolite in 1% carboxymethyl cellulose and a dermally applied cream containing of 10% silver zinc zeolite. ECHA concluded that considering that the type of silver zinc zeolite used was not specified and that co- formulants are expected to significantly impact dermal absorption, these results were not considered applicable to the active substance.
Despite the lack of relevant information on the toxicokinetics of silver zinc zeolite, it is assumed that the different constituents dissociate in the gastrointestinal tract prior to absorption. Therefore, the toxicokinetics of silver zinc zeolite may be estimated from data for each of the constituents.
According to published information (Fruijtier-Pölloth, 2009), zeolites may partially decompose during acidic conditions such as in the stomach and the intact molecule is not bioavailable after oral intake or through the dermal and inhalational routes.

After oral ingestion of sodium aluminium silicate, the major part is excreted in the faeces. A smaller part is hydrolysed in the digestive tract and a silicon compound is absorbed and excreted via the urine[15]. About 12% of the administered silicon dose is absorbed at doses between 40 and 200 mg/kg BW in rats (Benke and Osborne, 1979). A major part of the absorbed silicon is excreted within 24 hours and the half-life is between 6 and 8 hours in rats. The absorption of the aluminium component of the parent is less than 0.1% of the administered dose. A similar low rate of absorption for the aluminium component has been observed also in beagle dogs; however, the oral bioavailability of the silicon compound was lower than observed in the rat. Data on rats is considered most relevant for this assessment since the studies used to identify the critical NOAELs are conducted with this species.

Ref: HERA_Zeolite_01_2004

Silver

(Taken from SCCS/1577/16) Studies in humans and animals indicate that silver compounds are absorbed by the inhalation and oral routes and poorly by the dermal route. Absorbed silver is distributed widely throughout the body. Data on the extent of oral absorption is variable but is generally accepted to be relatively low. Juberg (1997) reports oral absorption values for silver in animal studies of less than 10%; WHO (2003) states that up to 5% of colloidal silver can be absorbed after oral exposure. Important factors in the absorption of silver include the presence and extent of silver-binding proteins and the solubility of the silver species (Juberg, 1997). Lansdown (2010) states that passive gastrointestinal absorption of the free silver ion is unlikely to be significant due to its reactivity with sulphydryl, carboxyl, hydroxy and protein ligands on mucosal surfaces and cell debris. Silver readily reacts with organic constituents of food, which further limits its absorption from the gastrointestinal tract. The extent of oral absorption is therefore variable but is estimated not to exceed 5-10% and is thought likely to be influenced by factors such as the presence of food and gastrointestinal transit time (ATSDR, 1990).

The systemic distribution of orally-absorbed silver is limited by extensive biliary excretion (first-pass effect) (Juberg, 1997). Absorbed silver is extensively bound to serum proteins including albumin and ceruloplasmin. Soluble silver ions may be deposited in tissues as insoluble salts such as silver chloride or silver phosphate (ATSDR, 1990); these insoluble salts are subsequently transformed to silver selenide and silver sulphide. Dermal silver deposits in one case of argyria were identified as being primarily composed of silver sulphide (Buckley et al, 1965). The characteristic blue or grey discoloration of skin exposed to sunlight in humans with argyria may be caused by the photoreduction of deposited insoluble silver salts to metallic silver (ATSDR, 1990). Studies in rat have also characterised silver deposits in internal organs as the silver sulphide (Berry & Galle 1982).

While deposition of silver has been observed in many organs and tissues, the liver and skin are identified as the main storage centres for silver in the body (ATSDR, 1990; Faust, 1992). Exposed experimental animals and humans show granular deposits containing silver in both pigmented and non-pigmented skin.

In studies using injections of radiolabelled metallic silver and silver nitrate in rats, the highest concentrations of silver were identified in the gastrointestinal tract, liver, blood, kidney, muscle, bone and then skin. The proportion of silver distributed to the tissues is positively correlated with the dose administered (ATSDR, 1990). Lansdown (2010) states that there is no convincing evidence for the passage of silver across the blood-brain-barrier or blood-CSF-barrier.

Zinc

(Taken from SCCS/1586/17) Generally, dermal exposure to water soluble zinc salts does not result in any noticeable toxic effects, with the exception of the skin irritancy that has been reported.

Most orally-ingested zinc is absorbed in the upper small intestine, although small quantities of zinc may be absorbed throughout the entire gastro-intestinal tract. Depending on the nutrition, absorption of zinc from the gastrointestinal tract varies between 8 to 80%. However,

in persons with an adequate zinc intake, the absorption varies between 20 to 30%. The major transporter of zinc in blood is albumin and virtually no zinc circulates in unbound form.
Zinc is found in all tissues of the body. In adults, the total body zinc is about 2.5 and 1.5 g in men and women, respectively. The majority of total body zinc is in the muscle and bone (ca 85%), in addition to skin and hair (ca 8%), liver (ca 5%) and in the gastrointestinal tract and pancreas (ca 3%). Only about 0.1% of zinc is circulating in the blood. In healthy subjects, plasma concentrations of zinc are affected by intake. However, homeostatic mechanisms that act to maintain plasma zinc concentrations within the physiological range may prevent high levels from being sustained over a prolonged period.
There is a rapid turnover of plasma zinc reflecting its exchange with all tissues and organs in the body. This exchanging pool of zinc fully exchanges with zinc in plasma and accounts for about 10% of total body zinc.
As zinc is present in the body as a bivalent cation, electrostatic interaction with anions and negatively-charged groups in proteins or other molecules is possible. However, as a metallic element, zinc is not metabolised.
About 70-80% of ingested zinc is eliminated with the faeces. However, the elimination rate depends on both zinc intake and status. There is a tight homeostatic control of zinc by the small intestine where the fundamental regulation factor is the targeted, transport-dependent absorption of zinc from the gut with a controlled discharge of endogenous zinc in the stool. Thus, in the case of a lack of zinc, endogenous extraction is reduced. Depending on zinc intake, between 14 to 25% is eliminated in the urine. Other elimination routes are via saliva, breast milk and sweat.
Oral intake of zinc may inhibit copper absorption through interaction with metallothionein at the brush border of the intestinal lumen. Both copper and zinc appear to bind to the same metallothionein protein, but copper has higher affinity than zinc. In humans, a disproportionate oral intake of zinc in relation to copper has been shown to induce copper deficiency resulting in increased copper requirements, increased copper excretion and impaired copper status. Adequate studies of chronic effects from lower levels of zinc on copper status are, however, not available.

3.2.1 Dermal / percutaneous absorption

According to the applicant, SZZ itself will not be absorbed following dermal application. Systemic exposure to the insoluble zeolite component will not occur; however, dermal absorption of the silver and zinc ions released from the substance may occur and is therefore considered.
The dermal absorption of silver (as a metal ion) is likely to be very low based on its physicochemical properties (lipid solubility and molecular weight) and interaction with dermal proteins (Hostynek, 2003). Skog & Wahlberg (1964) report the dermal absorption of silver nitrate through intact guinea pig skin to be less than 1%; Snyder (1975) reports a similar finding for human skin. Clinical studies also indicate that the dermal absorption of silver is 'exceedingly low' (Lansdown, 2010); this observation is attributed to the barrier properties of epidermal phospholipids and the irreversible binding of free silver ions to keratin sulfhydryl groups. More recent investigations of the dermal absorption of silver from impregnated dressings in burns patients report a level of dermal absorption of 0.1% or less, even in severely damaged skin (US EPA interpretation of data reported by Moiemen *et al.*, 2011). This level of absorption is orders of magnitude higher than that measured *in vitro* with intact or mildly damaged human skin (Larese *et al.*, 2009).
The SCCNFP (2003) concluded in their evaluation of zinc oxide that the dermal absorption of zinc was <1% based on the results of a study performed *in vitro* in pig skin with aqueous solutions of zinc sulphate and zinc oxide. The EU RAR also concludes that the dermal absorption of zinc oxide in intact skin is <2%. Minimal (but measurable) dermal absorption is also reported for zinc oxide nanoparticles applied to human skin in sunscreen formulations (Gulson *et al.*, 2012).

The dermal absorption of silver and zinc from the proposed use of SZZ in cosmetic products is likely to be low. For silver, a dermal absorption value of 0.1% is used as a conservative upper-bound estimate, which has previously been used in the calculation of systemic exposure resulting from dermal exposure to silver and margins of safety. For zinc, a reasonable worst-case dermal absorption value of 1% is used.

SZZ
A dermal penetration study, including a study on tape strippings, has not been provided. However, the SCCS agrees that based on its large crystalline structure, stability and absence of solubility, Silver Zinc Zeolite is unlikely to penetrate the human skin.

Silver
In its Opinion SCCS/1577/16, the SCCS considered the level of 0.1% dermal absorption to be relevant to 'EcoG+' and used it for the calculations of systemic exposure to silver resulting from the use of this product as cosmetic packaging material. The SCCS agrees with the Applicant's proposal to use 0.1% for the dermal absorption.

Zinc
In the absence of dermal penetration studies on water-soluble zinc salts releasing the Zn ion, the SCCS agrees with the Applicant's proposal to use 1% as dermal absorption value.

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

The preservative action of SZZ is mediated by silver ions, which migrate into the cosmetic product. The SZZ substances Ceramedic CW and Ceramedic CJ contain silver at levels of up to 2.5%. Ceramedic CW and Ceramedic CJ also contain zinc at levels of up to 13.5%. Ceramedic CW and Ceramedic CJ are proposed to be used in cosmetic products at a level of up to 1.0%.

3.3.2 Calculation of SED

Note: the Applicant supports only spray deodorant and powder foundation. Because dermal penetration by the zeolite itself is unlikely, only the exposure estimates for silver and zinc being released from the zeolite will be considered for the dermal component of the aggregate exposure.

Dermal exposure

Silver (based on the SSZ with the highest silver content):

Powder foundation: 7.9 mg/kg bw/d (SCCS Notes of Guidance).
SZZ content max 1% of which 2.5% is silver, of which 18% is released, equals 0.00025 x 0.18 x 7.9 = 0.00036 mg/kg bw/day.
SED: = 0.1% Derm Abs x 0.00036 = 0.00036 microgram/kg bw/d

Deodorant spray: 10.0 mg/kg/bw/d (SCCS Notes of Guidance). SSZ content max 1%, of which 2.5% is silver, of which 18% is released, equals 0.00025 x 0.18 x 10.0 mg/kg bw/d = 0.00045 mg/kg bw/d.
SED = 0.1% Derm Abs x 0.00045 = 0.00045 microgram/kg bw/d

Deodorant spray ethanol based: 20.63 mg/kg bw/d (SCCS Notes of Guidance). SZZ content max 1%, of which silver content is 2.5%, of which 18% is released, equals to 0.00025 x 0.18 x 20.63 = 0.0009 mg/kg bw/d.
SED = 0.1% Derm Abs x 0.0009 = 0.0009 microgram/kg bw/d

Deterministic aggregate *dermal* exposure, based on the aggregation with the higher value in the ethanol based deodorant spray:
SED = 0.00036 + 0.0009 = 0.00126 microgram/kg bw/d

Zinc
Powder foundation: 7.9 mg/kg bw/d (SCCS Notes of Guidance). SZZ content max 1% of which 13.5% zinc equals = 0.0013 x 7.9 = 0.01 mg/kg bw/day.
SED: = 1% derm Abs x 0.01 = 0.1 microgram/kg bw/d

Deodorant spray: 10.0 mg/kg/bw/d (SCCS Notes of Guidance). SSZ content max 1%, of which zinc 13.5% equals 0.00135 x 10.0 = 0.013 mg/kg bw/d.
SED = 1% derm Abs x 0.013 = 0.13 microgram/kg bw/d

Deodorant spray ethanol based: 20.63 mg/kg bw/d (SCCS Notes of Guidance). SZZ content max 1%, of which zinc content 13.5% equals 0.00135 x 20.63 = 0.028 mg/kg bw/d.
SED = 1% derm Abs x 0.028 = 0.28 microgram/kg bw/d

Deterministic aggregate exposure from *dermal* exposure, based on 100% zinc release from the matrix and based on the higher value in the ethanol based deodorant spray:
SED = 0.1 + 0.28 = 0.38 microgram/kg bw/d.

Inhalation exposure
Regarding inhalation, the exposure to spray deodorant (ethanol based) is considered relevant and will be used for the calculation of the aggregate exposure.

SZZ
Currently, there are no guidance values for the general population and no specific EU-wide occupational exposure limits for zeolites. Many countries, however, have regulated the maximum exposure to total dust and implemented limit values of 10 mg/m^3 for total dust and 3 or 5 mg/m^3 for respirable dust. (Fruijtier-Pollock 2009)

Silver
In the original submission, the Applicant made several assumptions for the calculation of the inhalation exposure resulting from spray deodorant use, and calculated for silver an SED of 0.0064 µg/kg bw/d.
Upon queries from the SCCS, the applicant submitted new exposure assessments using the ConsExpo model (RIVM ConsExpo Web, version 1.1.0, 26-10-2021).

According to the Applicant, this ConsExpo assessment assumes use of deodorant spray products 730 times per year (i.e., twice per day), with application for 0.17 minutes (10 seconds) and a mass generation rate of 0.45 g/s. This equates to daily product usage of 9 g/day. In contrast, the SCCS Guidance specifies product usage of 1.43 g/day for ethanol-based deodorant sprays and 0.69 g/day for non-ethanol-based deodorant sprays. The frequency of use parameter in ConsExpo is therefore modified to 365 times per year (once per day), with mass generation rates also modified to reflect the product usages listed in the SCCS Guidance and shown in the table below.

Product type	Product usage (g/d) (SCCS Guidance)	Frequency	Spray duration (minutes)	Mass generation rate (g/s)
Deodorant spray (not ethanol-based)	0.69	365/year	0.17	0.069
Deodorant spray (ethanol-based)	1.43	365/year	0.17	0.143

The following model parameters were used (abbreviated by the SCCS to parameters for alcohol-based deodorant spray, i.e. the higher exposure level, and the zeolite matrix with the highest silver content):

Body weight:	68.8 kg
Ventilation rate:	2 per hour
Inhalation rate:	9.23 L/minute
Product usage:	1.43 g/day (alcohol-based deodorant)
Spray duration:	10 seconds (0.17 minutes)
Exposure duration:	5 mins
Mass generation:	0.143 g/s (for alcohol-based spray). (Once daily use is assumed (spray duration 0.17 minutes); mass generation is therefore set to 0.143 g/s based on product usage of 1.43 g/d.)
Weight fraction:	0.025% (amount of silver in Ceramedic CJ)
Release from zeolite matrix:	18%

For silver released from the SZZ with the highest content (2.5%) in the ethanol-based deodorant spray (*i.e*. the conservative scenario), the model predicted for inhalation exposure an SED of 0.004 µg/kg bw/day for silver from SZZ.

SCCS comment
The Applicant wrongly used product use factors for spray deodorant that have been derived for dermal exposure by applying correction factors based on an experiment by Steiling *et al.,* 2012. For inhalation no worst-case fractions are available and, as a worst case, the SCCS assumes almost 100% availability. Moreover, a number of parameters used in the ConsExpo calculation from the Applicant have not been justified and/or are less conservative than suggested in the SCCS NoG (*i.e.* body weight, exposure duration, ventilation rate and inhalation rate).
Considering all these uncertainties together, in this specific case, the SCCS will apply a correction factor of 10 to the inhalation exposure estimate to account for the uncertainty regarding conservativeness of the proposed exposure estimates. Consequently, the SCCS will use an SED of 0.04 µg/kg bw/day for the calculation of the MoS.

The Applicant also submitted data on a fraction of the systemic exposure from ingestion of the ethanol-based deodorant spray. The SCCS has examined these data and considers this contribution to the total SED as negligible.

Zinc
In agreement with the conclusions in CAR-ECHA 2021 the SCCS will base the NOAEL on the effects observed from silver and not use the SED for zinc for the calculation of the MoS (see also 3.4.4.3).

3.4 TOXICOLOGICAL EVALUATION

According to ECHA (ECHA/BPC/275/2021), the toxicological studies available are performed with different types of silver zinc zeolites. These are not technically equivalent but read-across among the materials is considered justified.
The SCCS agrees with this approach.

3.4.1. Irritation and corrosivity

3.4.1.1 Skin irritation

According to the Applicant, the skin irritation potential of different forms of SZZ has been investigated in studies in the rabbit.
Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK) is reported to be a skin irritant. In a study performed in six rabbits, the mean (24-72 hour) scores for erythema and oedema do not trigger classification according to the CLP Regulation; however, the severity of the findings increased and were not reversible within the 14-day study period. In contrast, a study in the rabbit performed with Zeomic Type AJ10D SZZ (AgION® Silver Antimicrobial Type AJ) did not show any evidence of skin irritation.
The reason for the marked differences in irritant response between the different test materials is unclear. A correlation between silver content (2.5% in AgION® Type AJ; 4% in AgION® Type AK) and irritation level is noted. As the study with AgION® Type AJ followed an older design and used a 24-hour exposure period on abraded skin (both factors which would be likely to increase the irritant potential), it would appear that factors other than silver content influence irritation potential.

Ref: Nitka 2000-a, Kawasaki 1978

A further study (Gross 2018-a) performed using a human skin model (EpiDerm™) showed no irritant effects of SZZ (Ceramedic) after a 60-minute exposure time and a 42-hour post-incubation:

Guideline: OECD 439
Method: MTT reduction in Reconstructed human skin ('Epiderm')
Test material: Silver Zinc Zeolite, batch AJ0407 white fine powder
Concentration: 25 mg on top of 25 µL in sterile phosphate buffered saline.
Pre-test: no MTT reduction, no colouring
Exposure: 60 minutes
Control: Positive control 5% SDS; negative control phosphate buffered saline
Result: Mean tissue viability compared to negative control > 50% (94.6%), indicating non-irritancy.
Year: 2018
Ref: Gross 2018-a

According to the Applicant, zeolite substances are hygroscopic, a property which may influence skin irritation potential. It is possible, therefore, that SZZ may be a skin irritant *in vivo* due to its physical properties.
Some salts of silver (for example silver nitrate) are known to be corrosive or irritating (Juberg, 1997). Kim *et al.* (2012) reported an absence of dermal irritation in a study performed with nanosilver. The US EPA (EPA, 1992) concludes, based on animal data and experience of medical use of preparations containing silver, that sufficient data are available to conclude that silver itself is not a skin irritant. Similarly, some salts of zinc are known to be caustic (zinc chloride) or irritant (zinc sulphate), while other salts (zinc oxide) are non-irritating and are used to promote the healing of burns and wounds when topically applied as zinc oxide or calamine lotion. The low levels of silver and zinc attained in cosmetic products as a consequence of the proposed use of SZZ are therefore not predicted to result in skin irritation.

SCCS comment
Although, the *in vitro* guideline study with SZZ assessed in this Opinion shows no irritant properties, according to ECHA/BPC/275/2021 SZZ is classified as Skin Irrit. 2.

3.4.1.2 Mucous membrane irritation / eye irritation

According to the Applicant, the eye irritation potential of different forms of SZZ has been investigated in studies in the rabbit. In a study performed with Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK), the treated eyes of all three rabbits exhibited corneal opacity, iritis, conjunctival erythema and chemosis. The overall incidence and severity of the findings decreased and had resolved by 72 hours with the exception of conjunctival erythema, which persisted to Day 14. In a study performed with AgION Antimicrobial Type AD (Silver Zeolite), the treated eyes of all three rabbits exhibited corneal opacity, iritis, conjunctival erythema and chemosis. The overall incidence and severity of the findings decreased and had resolved by 72 hours.

Ref: Nitka 2000-b, Moore2006-b

A further study of the eye irritating potential of SZZ was performed on a human corneal epithelium model. It was determined that SZZ showed irritant effects.

Guideline:	OECD 492
Method:	Reconstructed human Cornea-like Epithelium (RhCE)
Test material:	Ceramedic Silver Zinc Zeolite, white fine powder (silver 2,5%, zinc 14.3%)
Batch:	AJ0407
Concentration:	50 mg as powder, directly atop the tissues.
Pre-test:	no MTT reduction, no colouring
Exposure:	6 hours
Control:	Positive control methyl acetate; negative control distilled water
Result:	Mean relative tissue viability (% negative control) ≤ 60% (41.2%). The test item showed irritant effects
Year:	2018
Ref:	Gross 2018-b

According to the Applicant, the marked difference in irritant responses seen in these studies is not believed to be attributable to the chemical composition of the test materials, which are essentially similar, but are due to the physical form in which the test material was administered. Zeolite substances are insoluble and hygroscopic and, consequently, have the potential to cause physical eye damage if administered in a dry form. This was the case for the studies performed with Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK) and Ceramedic, in which the most severe irritant effects were observed.
Some salts of silver (for example silver nitrate) are known to be corrosive or irritating (Juberg, 1997); however, Kim *et al.* (2012) report an absence of ocular irritation in a study performed with nanosilver. The EPA (1989) concludes, based on animal data and experience of the medical use of preparations containing silver, that sufficient data are available to conclude that silver itself is not an eye irritant. Similarly, some salts of zinc are known to be eye irritants whereas others have been in widespread clinical use without adverse effects. The low levels of silver and zinc attained in cosmetic products as a consequence of the proposed use of SZZ are unlikely to result in eye or mucous membrane irritation.

3.4.2 Skin sensitisation

SZZ

The skin sensitisation potential of different forms of SZZ has been investigated in studies in the guinea pig. A Buehler study performed with Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial type AK) reports a clearly negative result; clear negative results are also reported for a Maximisation study performed with Zeomic Type AJ10D SZZ (AgION® Silver Antimicrobial Type AJ). A Buehler study performed with AgION Antimicrobial Type AD (Silver Zeolite) reports an equivocal result due to the presence of very faint erythema in test and control animals.

The weight of evidence therefore indicates that SZZ is not a skin sensitiser. Although an equivocal response is reported in a Buehler study, it is notable that a clear negative response is reported in the (more sensitive) Maximisation assay.

Guinea pig sensitisation test (Buehler)

Guideline:	/
Method:	Buehler
Test material:	Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial type AK)
Induction:	100% pure, moistened with saline, 1x p week, 3 weeks
Challenge:	100% pure moistened with saline, two weeks after the last induction
Control:	DNCB (pos) and DMSO (neg)
Nr of animals:	13 received 3 inductions, 10 control animals without induction
Result:	no skin reaction
Year:	1999
Ref:	Nitka 2000c

Guinea Pig Maximisation test (GPMT)

Guideline:	Japanese guideline for toxicity Testing in Ethical Drugs, 1989
Method:	Magnusson & Kligman
Test material:	Zeomic Type AJ10N SZZ – silver-zinc-ammonium zeolite A, 2.2% Silver, 13.5% Zinc, 3.0% Ammonium
Induction:	2% in olive oil with FCA for intradermal, 40% in olive oil for patch induction.
Challenge:	10%, 1% and 0.1% in DNSO
Control:	DNCB (pos) and DMSO (neg)
Nr of animals:	10 for test material, 5 for pos control and 5 for neg control
Result:	no skin reaction
Year:	1996
Ref:	Matsuda 1996

Silver

According to the Applicant, despite the widespread and historic use of silver jewellery and the widespread use of silver salts in cosmetics, medical and personal care products, reports of skin sensitisation are infrequent and often associated with contaminants (e.g. nickel in silver jewelry). The US EPA (1989) states that sufficient data are available to conclude that silver itself is not a skin sensitiser.

Zinc

According to the Applicant, the EU Risk Assessment Report for zinc oxide (2004) concludes an absence of sensitisation potential for zinc salts based on a long history of clinical use. Sensitisation resulting from the use of SZZ is not predicted due to the low levels of silver and zinc attained in cosmetic products.

SCCS overall comment on skin sensitisation
Although there is no study report on sensitisation with the Applicant's AGZnZeolite, the tested analogues can be regarded as sufficiently similar, demonstrating that SZZ is unlikely to be a skin sensitiser.
ECHA (ECHA–CLH 2020) proposes to classify silver (ionic form) as a Skin Sens 1.
The SCCS agrees that reports of skin sensitisation are infrequent and often associated with contaminants (*e.g*. nickel in silver jewelry). The SCCS regards the risk of sensitisation from exposure to silver as negligible.
Although occasionally positive patch-test reactions to zinc have been reported, the clinical relevance of these reactions is unclear. Therefore, the SCCS regards the risk of sensitisation from exposure to zinc as unlikely.

3.4.3 Acute toxicity

3.4.3.1 Acute oral toxicity

SSZ
According to CAR-ECHA 2021, the LD50 values were above the limit dose of 2000 mg/kg bw in all studies, *i.e.* >2000 mg/kg bw for AGNION Antimicrobial Type AK and 5000 mg/kg bw for the unspecified type of silver zinc zeolite and AgION Antimicrobial Type AJ.

Silver
(Taken from SCCS/1577/16) Acute oral LD50 values for silver salts in mice are reported to be in the range 50-100 mg/kg bw (Faust, 1992; WHO, 2003). Acute oral LD50 values in the mouse of 100 mg/kg bw for colloidal silver and 129 mg/kg bw for silver nitrate; and acute oral LD50 values in the rat of 125 mg/kg bw for silver cyanide and >2820 mg/kg bw for the insoluble silver oxide are also reported (Faust, 1992). The US EPA (1992) stated that sufficient data are available to conclude that the acute toxicity of silver is relatively low.
A guideline- and GLP-compliant study of acute oral toxicity performed in the rat with nanosilver reports an LD50 value of >2000 mg/kg bw; no mortality or signs of toxicity were observed at the limit dose in this study (Kim *et al.*, 2013). Juberg (1997) states that acute oral LD50 values of silver compounds including silver nitrate, silver oxide, silver fluoride and silver chloride are indicative of slight to moderate toxicity.

3.4.3.2 Acute dermal toxicity

The acute dermal LD50 of Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK) and Zeomic Type AJ10D SZZ (AgION® Silver Antimicrobial Type AJ) are both reported to be >2000 mg/kg bw.

Summary of acute dermal toxicity data for SZZ:

Test material		
Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK)	LD50 >2000 mg/kg bw	Moore GE (2000b)
Zeomic Type AJ10D SZZ (AgION® Silver Antimicrobial Type AJ)	LD50 >2000 mg/kg bw	Shimizu Y (1987)

According to ECHA-CLH (2020) the acute dermal toxicity for silver is above 2000 mg/kg/bw.

3.4.3.3 Acute inhalation toxicity

According to the Applicant, the acute inhalation toxicity of one form of SZZ has been investigated; the study demonstrates low acute inhalation toxicity. The acute inhalation LC50 of Zeomic Type AK10D SZZ (AgION® Silver Antimicrobial Type AK) is reported to be >2.86 mg/L (Leeper 2000). The available data therefore demonstrate low acute inhalation toxicity for SZZ. No reliable data have been identified for the acute inhalation toxicity of silver or silver salts. Acute human inhalation exposure to very high concentrations of zinc chloride smoke has been associated with toxicity and mortality; however other components of the smoke and the caustic nature of zinc chloride may have been contributory factors. Metal fume fever is also reported in workers exposed to high concentrations of ultrafine particles of zinc oxide formed by heating zinc beyond its boiling point in an oxidising atmosphere. Metal fume fever is characterised by temporarily impaired pulmonary function that does not progress to chronic lung disease. This condition is not relevant to the proposed use of SZZ.

Silver
According to ECHA-CLH (2020) the LC50 is above 5.16 mg/L air

3.4.4 Repeated dose toxicity

3.4.4.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

3.4.4.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity

A 90-day dog oral toxicity study was performed with AgION Silver Antimicrobial AK at dose levels of 10, 50 and 250 mg/kg bw/d; the test material was administered in capsules. Clinical signs (including salivation, head shaking and vomiting) were observed at the highest dose level and were considered by the Study Director likely to be related to the taste of the test material. Haematology revealed reduced haemoglobin concentrations in both sexes at the highest dose level; clinical chemistry analyses revealed increased cholesterol concentration and increased serum alkaline phosphatase activity. At necropsy, discoloration of the gastrointestinal tract and pancreas were observed at the high-dose level of 250 mg/kg bw/d. Histopathological investigations showed effects on the kidney, including an increased severity of corticomedullary tubular basophilic and lymphoid infiltration, interstitial fibrosis and hyaline/cellular casts at 250 mg/kg bw/d. A NOAEL of 50 mg/kg bw/d was therefore determined for this study.
Ref: Teunissen 2003.

According to CAR-ECHA 2021, the overall subchronic NOAEL for the types of silver zinc zeolites used in representative formulations of 50 mg/kg bw/day is based on pigmentation, increased level of ALP, effects on haematological parameters and effects on behaviour/ activity observed in dogs administered 250 mg AgION Antimicrobial Types AK /kg bw/day.

3.4.4.3 Chronic (> 12 months) toxicity

SZZ
Combined chronic toxicity/carcinogenicity study in mice and rats (Takizawa 1992).
The test material Zeomic AJ 10N was an odourless crystalline powder with the Ag, Zn, and NH4 contents of 2.3%, 12.5%, and 2.5%, respectively. The test substance, which was mixed with a commercial diet, was administered to both male and female dosing groups (75 BC3F1 mice and 70 Fischer 344 rats per sex per dose level) in feed at levels of 0.1%, 0.3%, and 0.9%, in the mice study, and 0.01%, 0.03%, 0.1%, and 0.3% in the rat study. The control groups were given a similarly prepared diet without the test substance. Mice were sacrificed

as follows: 5 per sex per dose level at 3 months, 10 at 6 months, 10 at 12 months, and 50 at 24 months. Ten rats per sex per dose level were sacrificed at 6 months, 10 at 12 months, and 50 at 24 months.
Autopsy was performed in 5 overnight-fasted animals of each group at 3 months (mice), and 10 animals at 6, and 12 months after the beginning of dosing (rats and mice). Those that became moribund during the observation period were sacrificed and the autopsy findings were recorded. The remaining animals were observed until the end of the 24-month dosing period. Each animal was observed once daily with regard to general condition and death. Food intake was measured and recorded once a week, while body weight was measured once a week for the first 53 weeks and once every two weeks after week 53. Clinical chemistry and hematology data were recorded for interim and terminal sacrifices.

The cumulative survival rate and the mean survival time in treated animals and controls were similar. Clinical signs were not tabulated and the information is limited to a sentence stating that abdominal and subcutaneous masses and corneal clouding was observed in all rats (including controls) while pigmentation of skin was noted in treated animals. Increased levels of liver enzymes (AST, ALT and LDH) and hepatic bile duct proliferation were observed in all treated rats, indicating that the liver is a target organ. The total count of white blood cells was 2-5 times higher in high dose males and females at 24 months. Effects on haematological parameters (decrease in HCT, Hb (12%), MCH and MCHC) were observed at 24 months in the two highest dose levels in females, but there were no effects in males.
There were no effects observed in any of the treated animals at 6 and 12 months or among animals in the lower dose groups at 24 months.
The pathological examination revealed pigmentation of liver, kidneys, pancreas, stomach, lymph nodes and the choroid plexus in high-dose rats.

According to CAR-ECHA 2021, the chronic NOAEL, derived from the above-mentioned oral dosing study in rats, based on pigmentation as a critical effect, is considered to be 9 mg AgION Type AJ/kg bw/day or 0.09 mg silver ion equivalents/kg bw). With correction for absorption from the stomach of 5%, this would imply a NOAEL for silver of 0.0045 mg (4.5 microgram)/kg bw/d

Silver
The Applicant summarised the toxicological reference values for silver as follows:
All published reviews agree that the critical effect of silver exposure is argyria. Toxicological reference values for silver have been derived by the EPA, WHO and EFSA, as discussed below.
The US EPA uses a systemic lifetime (systemic) exposure of 1 g silver as a starting point; this is calculated to be equivalent to a systemic exposure level of 0.00056 mg/kg bw/d (0.56 µg/kg bw/d), assuming a lifetime of 70 years and a bodyweight of 70 kg.
Using epidemiological and pharmacokinetic data, WHO (2003) derives a human NOAEL (lifetime oral intake) for silver of 10 g, corresponding to 0.39 mg/day or 0.0065 mg/kg bw/d. Assuming a gastrointestinal absorption of silver of 5%, this is equivalent to a systemic reference value of 0.000325 mg/kg bw/d (0.325 µg/kg bw/d), a value comparable to that derived by the US EPA.
EFSA has evaluated silver-based preservatives for use in food-contact materials on the basis of human and animal data and has derived a group restriction limit of 0.05 mg/kg food, which corresponds to a worst-case exposure of 0.05 mg/day or 0.00083 mg/kg bw/d. Assuming a gastrointestinal absorption of silver of 5%, this is equivalent to a systemic reference value of 0.0000415 mg/kg bw/d (0.0415 µg/kg bw/d).

Zinc
According to the applicant, zinc is an essential dietary element; therefore, as a first tier, exposure to zinc resulting from the proposed cosmetic use is compared against the average requirements and population reference intakes for dietary zinc defined by EFSA in 2014.
The lowest PRI value for adults of 7.5 mg/day is used in this assessment, for comparative purposes. Based on the dietary availability of zinc of 30% (EFSA, 2014) and assuming

bodyweight of 60 kg, this is equivalent to a systemic exposure of approximately 0.42 mg/kg bw/d.

(From ECHA registration dossier – key study) Based on a study with zinc monoglycerolate the NOAEL is 31.52 mg/kg bw (»13.26 mg Zn^{2+}/kg bw).
Besides animal data, there are several human studies in which humans were supplemented with moderately high amounts of zinc (50 mg Zn/day) (as zinc gluconate). The EU Risk Assessment Report Zinc Oxide (2004) sets a NOAEL of 50 mg Zn^{2+} / day, which equals 0.83 mg Zn^{2+}/kg bw/day.

From SCCS on zinc in oral products (SCCS/1586/17):
Based on an oral zinc intake level where no effects on parameters of the copper balance occur, a NOAEL of 0.43 mg zinc/kg body weight and day (corresponding to 25.8 mg/day for an adult with a body weight of 60 kg) after oral intake was defined by Hartwig *et al.* (2014).
An UL of 25 mg zinc/day also applies to pregnant and lactating women. The following ULs were extrapolated by SCF for children and young people: 1-3 yrs: 7 mg/day; 4-6 yrs: 10 mg/day; 7-10 yrs: 13 mg/day; 11-14 yrs: 18 mg/day, 15-17 yrs: 22 mg/day.

Inhalation of zeolites
According to ECHA-CLH (2020), silver is not considered a respiratory sensitiser.
In the context of exposure to zeolites type A from laundry detergent powder, a risk assessment was performed by a conglomerate of representatives from industry (HERA 2004). According to this report, long-term inhalation studies with sodium aluminium silicate dust have been performed in the rat, the guinea pig, the hamster and the monkey. The available information on the mean diameter of the dust particles indicates that a large fraction of the generated dust has reached the lungs in these studies. Despite a number of deficiencies in the quality, the studies failed to produce any evidence of systemic toxicity, fibrosis or an increase in the incidence of neoplastic changes.
The monkey study is the best-documented inhalation study, which is also most relevant to the human risk assessment. With regard to local effects in the respiratory tract, the upper airways were not affected by the inhalation exposure. The histopathological effects observed in the lungs were macrophage accumulations accompanied by sporadic nonsuppurative bronchiolitis and alveolitis. No evidence of progressive pulmonary fibrosis was observed. Hence, sodium aluminium silicate dust is regarded as a poorly soluble non-fibrogenic dust with regard to human inhalation risk. Dose-related nonsuppurative inflammatory reactions were observed in animals of all dose groups. These reactions had diminished in severity but had not fully disappeared in the mid- and high-dose group. In the 1 mg/m³ dose group, these effects were not evident after the 90-day recovery period. The LOAEL for inhalation is 1 mg/m³.

Ref: HERA 2004

SCCS overall comment on chronic toxicity
In agreement with the conclusions in CAR-ECHA 2021 the SCCS will base the NOAEL on the effects observed from silver and set this at 0.0045 mg/kg bw/d. This will be used for the calculation of the MoS.

3.4.5 Reproductive toxicity

3.4.5.1 Fertility and reproduction toxicity

SSZ
A two-generation reproduction and fertility study of Zeomic (silver zinc zeolite) has been performed with oral gavage doses of 200, 700, 2000 mg/kg bw/day in Rats (Schroeder 2002) According to CAR-ECHA (2021), there is only substance-specific data available for this Silver Antimicrobial Type AK (Schroeder 2002). It was concluded that silver zinc zeolite does not affect fertility at doses up to 12500 ppm (984/1109 mg/kg bw): the NOAEL for reproduction is 1000 ppm (approximately 70 mg Type AK/mg kg bw).

Silver
(Taken from ECHA-CLH (2020) The data available on silver acetate and nanosilver indicate that the silver ion has the ability to cause adverse effects on sexual function and fertility possibly by a mechanism involving oxidative stress. According to the original report for the silver acetate study and the published studies with nanosilver, there were no marked general toxicity indicating that effects were "a non-specific consequence of the other toxic effects".

3.4.5.2 Developmental Toxicity

SZZ
From the above-mentioned two-generation reproduction and fertility study of silver zinc zeolite (Schroeder 2002), the RAC concluded that the enlargement of hearts reported at the mid dose in F2 pups (5/27 males and 4/26 females) appeared in the presence of mild maternal toxicity (mainly hydronephrosis and haematological alterations) and cannot be totally disregarded for classification. This same effect also appeared in F1 pups at the highest dose (6/14 males and 6/18 females), albeit in the presence of excessive maternal toxicity. The RAC considered these effects on the heart as relevant for classification of SZZ as toxic to development Cat 2.

Silver
(Taken from SCCS/1577/16) A high-quality developmental toxicity study performed in the rat with silver acetate (NTP, 2002) concludes a NOAEL for developmental toxicity of 100 mg/kg bw/d, the highest dose level tested. Indications of slight maternal toxicity were observed at this dose level; more severe maternal toxicity was observed at a dose level of 160 mg/kg bw/d in a screening study. Published data (Shavlovsky *et al.*, 1995) indicate an effect of silver on development at maternally toxic dose levels and secondary to copper deficiency caused by the displacement of copper by silver from ceruloplasmin.

Zinc
(Taken from SCCS/1586/17) In animal studies on Zn sulphate, no potential for prenatal developmental toxicity was found at the doses of 200 mg/kg bw/day in rats and 6.8 mg/kg bw/day in mice (highest doses tested). In a number of studies with healthy pregnant women, a daily oral zinc supplement of 20-90 mg has shown no indication of adverse effects.
While there is some evidence for the developmental toxicity of ingestion of zinc chloride at high-dose levels (Johnson 2011), adverse effects will not occur at levels of exposure that are within the normal background levels of dietary exposure for this essential element.

SCCS comment
The SCCS agrees with ECHA/BPC/275/21 that silver zinc zeolite fulfils criteria for classification Repr. 2; H361d. The NOAEL derived from the chronic toxicity study (see 3.4.4.3) is far below the NOAEL for reproductive and developmental effects.

3.4.6 Mutagenicity / genotoxicity

3.4.6.1 Mutagenicity / genotoxicity *in vitro*

SZZ
(Taken from CAR-ECHA 2021)
The data available to assess the *in vitro* mutagenicity of silver zinc zeolite include studies performed with two forms of silver zinc zeolite; AgION Antimicrobial Type AK and Irgaguard 8000 as well as with an unspecified form assumed to be equivalent to Irgaguard 8000. The two Ames salmonella mutagenesis assays were both negative, whereas positive responses were obtained in the two mutation assays performed in mammalian cells (TK-locus tests) with AgION Antimicrobial Type AK (with and without S9) and silver zinc zeolite (assumed to be Irgaguard 8000) (without S9). The negative response in presence of the S9 mix may be due to silver ions binding thiol groups and other functional groups of proteins in the S9 mix. The positive response was shown as a reproducible increase (3-fold) in the number of mutant colonies at the highest dose in the experiments. In addition, there was an increase in the number of small colonies in the study with Irgaguard 8000, indicating a possible clastogenic activity. A clastogenic response was also observed in the chromosomal aberration assay performed with Irgaguard 8000 (in the absence of metabolic
activation).

Silver
(Taken from SCCS/1557/16) The genotoxicity of Ag^+ ions was investigated for all the three endpoints of genotoxicity: gene mutations, chromosome aberrations and aneuploidy, although results from mammalian cell gene mutation tests were not provided. The available tests were not always performed according to present standards and the data obtained are generally inconclusive. Ames test data are of limited value due to strong bactericidal properties of Ag^+ ions. Gene mutation tests in mammalian cells are not provided. Results on chromosomal damage show negative and positive results.
As Ag^+ ions are released from silver nanoparticles and as one of the toxicity mechanism of silver nanoparticles (AGNPs) is via Ag^+ ions, the genotoxicity of AgNPs was considered as well. Genotoxicity/ mutagenicity data on AgNPs are also inconclusive, showing both positive and negative effects. Due to different amounts of Ag^+ ions released from different AgNPs, these data can only be tentatively considered.
As the main mechanism of genotoxicity of silver ions is via ROS production, which is an indirect and concentration dependent process, and since the concentrations of silver ions present in cosmetic products are low, the SCCS has no concern with regard to human risk.

Zinc
(Taken from SCCS/1586/17) Existing data on genotoxicity/mutagenicity of zinc salts (zinc acetate and zinc chloride) are inconclusive, showing mostly negative but in some cases positive effects. There is an indication of genotoxic/mutagenic/clastogenic potential of zinc ions (released from zinc oxide nanoparticles) *in vitro* and *in vivo,* acting most likely via secondary mechanisms, *e.g*. via oxidative stress and inflammation, and thus considered threshold-dependent. Based on the available data, SCCS concludes that the available evidence is insufficient to consider the evaluated zinc salts as genotoxic.

3.4.6.2 Mutagenicity / genotoxicity *in vivo*

SZZ
(Excerpts taken from CAR-ECHA 2021): The *in vivo* mutagenicity of a type of silver zinc zeolite assumed to be Irgaguard 8000 was investigated in a micronucleus assay. No significant increase in chromosomal aberrations was observed but there were no signs of toxicity at the target tissue and no clinical signs of systemic toxicity, thus it is uncertain whether or not the bone marrow actually was exposed to silver zinc zeolite to an extent that is meaningful for

genotoxicity testing. Furthermore, the sampling times used in the study (6, 18, and 24 h post exposure) were not optimal. According to the OECD guideline, samples should be taken at two separate times following treatment on one day. For rodents, the first sampling interval is 1.5 normal cell cycle length (the latter being normally 12-18 hr) following treatment. Since the time required for uptake and metabolism of the test substance as well as its effect on cell cycle kinetics can affect the optimum time for chromosome aberration detection, a later sample collection 24 hr after the first sample time is recommended. In essence, this implies that only by using a sampling time after 24 hours it would be possible to detect any genotoxic effects (under the prerequisite that a sufficient amount of the test substance reached the target tissue). Hence, a sampling time later than 24 hours would have been preferable. Finally, only 50 metaphase cells were scored per animal whereas the OECD guideline recommends scoring of at least 100 metaphase cells.
Considering that silver is excreted in bile and the estimated oral absorption is only 5%, the *in vivo* micronucleus test via the oral route seems to be unsuitable for investigating the genotoxic potential of silver. Therefore, the results from the *in vivo* chromosome aberration assays are considered insufficient to dismiss the concern for genotoxicity raised from the *in vitro* studies.
To further address the possible *in vivo* genotoxic potential of silver zinc zeolite, the applicant conducted an (*in vivo*) alkaline comet assay. The alkaline comet study was performed in rat using a silver zinc zeolite denoted Hygentic 8000.
Male rats received 0, 500, 1000 or 2000 mg/kg bw (administered as 2 doses separated by 21 hours). Positive controls received ethyl methanesulphonate. The tissues selected for comet analysis included the liver (as the primary organ for metabolism) and the stomach and duodenum (as the key sites of contact following oral administration).
The results of the analyses of liver, stomach and duodenum in treated animals were comparable with the group mean vehicle control data (i.e. no statistically significant increases in tail intensity between treated and control groups).
Some microscopic changes related to administration of the test article were observed in the stomach and liver and an increase in mean glucose concentration was also observed. These changes were not considered to impact on the comet analysis of the tissues. Based on these results, Hygentic 8000 does not induce DNA damage in the liver, stomach or duodenum of male rats following oral administration of doses up to 2000 mg/kg bw (the maximum recommended dose for *in vivo* comet studies).
It should be noted that Hygentic 8000 (also denoted Irgaguard B 8000 and Bactekiller AZ) contains less silver and zinc compared to the types of silver zinc zeolites considered in this assessment and is thus not completely representative.
Since the same type of silver zinc zeolite was tested *in vitro* in a mammalian cell mutation test in mouse lymphoma L5278Y cells and in a chromosome aberration test in Chinese Hamster V79 cells (see section 3.8.1) and the results are in accordance with those obtained with one of the representative types (AgION antimicrobial Type AK) and the result in the comet assay was clearly negative, the deficiency with respect to test material is not expected to invalidate the overall conclusion.
Consequently, the applicant has fulfilled the data requirement to follow up positive *in vitro* findings with an appropriate *in vivo* assay and based on the negative result obtained, silver zinc zeolite is not considered genotoxic *in vivo*.

SCCS comment
The SCCS agrees with ECHA/BPC/275/2021 that the genotoxic potential of the substance has been adequately investigated *in vitro* and *in vivo*. While the *in vitro* test in mammalian cells indicated a mutagenic potential of silver zinc zeolite, there were no indications of genotoxicity in the *in vivo* studies conducted, which overrules the positive *in vitro* findings.

3.4.7 Carcinogenicity

SSZ
A combined chronic/carcinogenicity study (Takizawa 1992, see also 3.4.4.3) performed with silver zinc zeolite (AgION Antimicrobial Type AJ) found no difference in incidence between the different dose groups and control group. The CAR-ECHA 2021 report considered that the results from this study do not meet the criteria for classification.
A further ECHA Opinion (ECHA/BPC/275/2021) also stated that, based on information on chronic toxicity and carcinogenicity of silver zinc zeolite, classification is not warranted.

Silver
According to SCCS/1577/16 and ECHA-CLH (2022) silver is not carcinogenic.

Zinc
(Taken from SCCS/1586/17) Studies on zinc-induced carcinogenicity have not demonstrated increased cancer incidence after long-term exposure.

SCCS comment
The SCCS agrees with the ECHA Opinion (ECHA/BPC/275/2021) that silver zinc zeolite is not likely to be carcinogenic.

3.4.8 Photo-induced toxicity

3.4.8.1 Phototoxicity / photo-irritation and photosensitisation

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3.4.8.2 Photomutagenicity / photoclastogenicity

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3.4.9 Human data

Zeolites
According to a review of the safety of zeolites used in detergents, no systemic toxicity is to be expected under current conditions of manufacture and use (Fruijtier-Pölloth 2008).

Silver
(Taken and abbreviated from SCCS/1577/16; for references, see that Opinion)
Silver has no known physiological function (Faust, 1992). The WHO (1977) estimates the oral intake of silver for humans from dietary sources to range from 27-88 µg/day; intake via drinking water may contribute a small amount to this figure. A small but measurable amount of silver is accumulated by individuals over their lifetime. The EPA (1996) concluded that the critical effect in humans exposed to silver is argyria, a benign but possibly permanent blue-grey discoloration of the skin resulting from the deposition of silver in the dermis. Although silver is uniformly deposited in the skin, pigmentation may be more pronounced in areas exposed to sunlight due to photo-activated reduction of the metal and the stimulation of melanin production by silver (Greene & Su, 1987; Wadhera & Fung, 2005). Although the deposition of silver is permanent, it is not associated with any adverse health effects (EPA, 1996), pathological or inflammatory changes (Greene & Su, 1987). Lansdown (2010) also notes that argyria is not associated with cellular or tissue damage and is widely considered not to be of toxicological significance. Widespread argyria has been observed following the prolonged use of high levels of colloidal silver by humans, and has also been reported in

experimental animals administered silver compounds. Following systemic absorption, the deposition of silver is apparent in internal organs; however, the evidence indicates that silver does not cross the blood-brain-barrier or the blood-CSF-barrier (Lansdown, 2010). Relatively high concentrations of silver are reported in the liver, and may be associated with transient changes in clinical chemistry parameters but not with any evidence of pathological damage in patients with severe argyria or in animal models. The EPA uses the lowest dose resulting in argyria in one patient reported in a case series by Gaul & Staud (1935) of 4 g silver arsphenamine (equivalent to 1g silver) to be a minimal effect level for argyria. Workers exposed to silver as a consequence of work in the manufacturing and packaging of silver nitrate (mining, smelting, polishing and hammering of silver) are reported to show generalised argyria. Localised argyria may also be manifested as isolated areas of pigmentation occurring at the tracheobronchial junction the smaller bronchi (Faust, 1992). Large oral doses of silver nitrate have been reported to cause abdominal pain, diarrhoea, vomiting, shock, convulsions and death (Faust, 1992); however, effects are attributable to the corrosive properties of this form of silver. The estimated fatal dose in humans is 10 g. Juberg (1997) states that the results of several occupational epidemiology studies have not revealed any adverse health effects in workers exposed by inhalation to metallic silver, soluble and insoluble salts of silver for periods of 5-20 years. Studies demonstrated pigmentation of the skin, eyes (conjunctivae) and mucous membranes and elevated silver concentrations in the blood, faeces and hair but no evidence of haematological change or clinical chemistry indications of organ damage. The dermal absorption of silver compounds in intact human skin is low, but may be greater in burns patients (ATSDR, 1990). Silver was detected in the urine, blood, and body tissue of humans with seriously burned skin following treatment with topical preparations containing silver nitrate. Distribution into muscle, liver, spleen, kidney, heart and bones has been demonstrated following the topical application of silver nitrate for the treatment of burns.

Besides two case reports on a formulation with colloidal silver, there are no studies available on respiratory sensitisation (ECHA-CLH 2020).

Zinc
Zinc is an essential dietary element involved in many biochemical processes; and is critical for the maintenance of normal immune, sexual and neurosensory function such as cognition and vision. Adverse effects of zinc supplementation (as zinc sulphate) at a level of 150 mg/day are reported to be headache, nausea and gastric discomfort. The EU RAR for zinc concludes that 50 mg/day constitutes a human oral NOAEL for zinc. The EU RAR also concludes that there is no clear evidence for the mutagenicity or carcinogenicity of zinc. Zinc deficiency is associated with the impairment of fertility and foetal development; however, evidence from animal studies also indicates that high levels of exposure to zinc (≥200 mg/kg bw/d) may also cause adverse effects on fertility and foetal development. The EU RAR concludes that, as the reproductive effects seen in animal studies are seen only at high-dose levels associated with general toxicity and are approximately 80 times higher than the dose levels causing side effects in humans, it is unlikely that effects will be manifest in humans at dose levels that do not cause clinical signs. Fertility and developmental toxicity are therefore not considered to be endpoints of concern for humans. Zinc can interact with other trace elements, especially copper, resulting in toxicity which is usually due to depletion of these elements, leading to nutritional deficiencies. Effects are generally seen following repeated exposure to high levels of zinc.

3.4.10 Special investigations

No robust information is available to assess the neurotoxic or immunotoxic potential of silver zinc zeolite. However, the available data do not show clear indications of such properties.

An assessment of the endocrine disrupting (ED) properties was conducted. This assessment could not be finalised by ECHA as the data were considered insufficient for an assessment

against the criteria laid down in Regulation (EU) No 2017/2100. No further report was provided in this regard for this submission.

Ref. ECHA/BPC/275/2021

SCCS comment
The SCCS has not been able to assess potential ED effects of SZZ due to lack of relevant information.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS, BASED ON EXPOSURE TO SILVER)

Dermal exposure, aggregated for powder foundation and ethanol-based spray:

Systemic exposure dose-SED (see 3.3.2): 0.00126 microgram/kg bw/d
No observed adverse effect level-NOAEL: 4.5 microgram/kg bw/d (see 3.4.4.)

Margin of Safety (NOAEL/SED) =	3570

Inhalation exposure:

Systemic exposure dose-SED (see 3.3.2): 0.04 microgram/kg bw/d
No observed adverse effect level-NOAEL: 4.5 microgram/kg bw/d (see 3.4.4.)

Margin of Safety (NOAEL/SED) =	112

Deterministic aggregated dermal and inhalation exposure:

Systemic exposure dose-SED (see 3.3.2): 0.00126 + 0.04 = 0.04126 microgram/kg bw/d
No observed adverse effect level-NOAEL: 4.5 microgram/kg bw/d (see 3.4.4.)

Margin of Safety (NOAEL/SED) =	109

3.6 DISCUSSION

Physicochemical properties

This Opinion concerns two forms of synthetic Silver Zinc Zeolite, LTA1 framework type, surface-modified with silver and zinc ions. The silver content of the two forms are 0.55% and 2.5% respectively, while the zinc content of both forms is 13.5%.

The zeolite particles are not considered as nano materials

The zeolite core is considered stable and insoluble, besides the intentional release of silver and zinc ions in an aqueous environment. Based on the provided solubility reports regarding sufficiently similar zeolites, the release of silver in physiologic media is considered to be maximally 18%.

Toxicokinetics

SZZ itself will not be absorbed following dermal application but dermal absorption of the silver and zinc ions released from the substance may occur.

Despite the lack of relevant information on the toxicokinetics of silver zinc zeolite, it is assumed that the different constituents dissociate in the gastrointestinal tract prior to absorption. Therefore, the toxicokinetics of silver zinc zeolite may be estimated from data for each of the constituents.

The extent of oral absorption is therefore variable but is estimated not to exceed 5 - 10% and is thought likely to be influenced by factors such as the presence of food and gastrointestinal transit time.

The systemic distribution of orally absorbed silver is limited by extensive biliary excretion. Absorbed silver is extensively bound to serum proteins including albumin and ceruloplasmin. Soluble silver ions may be deposited in tissues as insoluble salts such as silver chloride or silver phosphate; these insoluble salts are subsequently transformed to silver selenide and silver sulphide.

Zinc is present in all body tissues. In healthy subjects, plasma concentrations of zinc are affected by intake. However, homeostatic mechanisms that act to maintain plasma zinc concentrations within the physiological range may prevent high levels from being sustained over a prolonged period.

There is a rapid turnover of plasma zinc reflecting its exchange with all tissues and organs in the body. This exchanging pool of zinc fully exchanges with zinc in plasma and accounts for about 10% of total body zinc. Depending on oral zinc intake, between 14 to 25% is eliminated in the urine. Other elimination routes are via saliva, hair, breast milk and sweat.

Exposure

Because of its large crystalline structure, stability and absence of solubility, dermal exposure will not result in absorption of silver zinc zeolite, but absorption of the silver and zinc ions released from the substance may occur. Systemically available silver from dermal and inhalation exposure is considered to be the most toxicologically relevant and therefore the toxicological evaluation will be based on the systemic exposure dose of silver.

Based on earlier evaluations by the SCCS, a value of 0.1% dermal absorption is used for the calculation of the systemic exposure to silver. Based on solubility reports, a release of 18% of the silver from the zeolite matrix with the highest (2.5%) silver content will be used, also for the calculation of the systemic exposure from inhalation.

Deterministic dermal and inhalation exposure based on the use of the zeolite with the highest silver content is used for the calculation of the margin of safety.

Toxicological Evaluation

Synthetic zeolites are extensively used in household detergents; no systemic toxicity is to be expected under current conditions of manufacture and use. Toxicological studies with different types of silver zinc zeolites are available. The SCCS concurs with ECHA that although these are not technically equivalent, they are considered sufficiently similar to justify read-across.

Because exposure to silver is considered to be toxicologically the most relevant, the evaluation is focused on this compound. The release of zinc from silver zinc zeolite as used in the product categories proposed in this evaluation is considered to be not toxicologically relevant.

Irritation and corrosivity
An *in vitro* guideline study with SZZ shows no skin irritant properties. The positive result of a guideline eye irritation study is most likely due to the physical form of the test material and not to its chemical composition.

Skin sensitisation
Tests in guinea pigs indicate that silver zinc zeolite is unlikely to be a skin sensitiser. Although silver is proposed to have a classification as Skin Sens 1, the SCCS regards the risk of sensitisation from exposure to silver from silver zinc zeolite as negligible.

Repeated dose toxicity
The NOAEL used in this evaluation (0.0045 mg/kg bw/d) is derived from a combined chronic (up to 24 months) toxicity/carcinogenicity study in mice and rats that were fed with a silver zinc zeolite containing 2.3% silver and is based on pigmentation as a critical effect from silver release.

Inhalation toxicity
An industry-led risk assessment regarding zeolites type A from laundry detergent powder concluded for inhalation a LOAEL of 1 mg/m^3. Inhalation studies with silver zinc zeolite are not available. Therefore, the SCCS modelled the inhalation exposure from the usage proposed by the Applicant, and based its safety assessment, in view of the apparently low inhalation toxicity from the zeolite itself, on the release of silver in the airways.

Reproductive toxicity
At gavage doses up to approx. 1000 mg/kg bw, silver zinc zeolite does not affect fertility. However developmental effects (pup mortality, decreased pup weight and cardiac effects) were noted and ascribed to the effects from silver. According to ECHA/BPC/275/21, silver zinc zeolite fulfils criteria for classification Repr 2; H361d. The NOAEL derived from the chronic oral toxicity study (which is used in the current assessment) is amply below the NOAEL for reproductive and developmental effects.

Mutagenicity / genotoxicity
The SCCS concurs with the ECHA Opinion (ECHA/BPC/275/2021) that the mutagenic potential of the substance has been adequately investigated *in vitro* and *in vivo*. While the *in vitro* test in mammalian cells indicated a mutagenic potential of silver zinc zeolite, there were no indications of genotoxicity in the *in vivo* studies conducted, thereby overruling the positive *in vitro* findings.

Carcinogenicity
According to previous SCCS Opinions, silver (and zinc) are not considered carcinogenic. A long-term carcinogenicity study with silver zinc zeolite in mice and rats did not note an increased incidence of malignancies. Therefore, silver zinc zeolite is not regarded as carcinogenic.

Human data
Observations in humans exposed to higher doses of silver compound indicate a relatively low toxicity. The observations support the use of exposure data from silver released by silver zinc zeolite as a parameter for the safety assessment.

Special investigation
There are no reports that point towards a neurotoxic, immunotoxic or endocrine disrupting potential.

4. CONCLUSION

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the classification as Toxic for reproduction Cat. 2, does the SCCS consider Silver Zinc Zeolite safe when used as a preservative in cosmetic products according to the specifications and concentration limits provided in the dossier submission?*

   The SCCS considers that Silver Zinc Zeolite (CAS No. 130328-20-0) incorporating a maximum silver content of 2.5% is safe in spray deodorant and powder foundation when used at the proposed concentration of 1%.

2. *Alternatively, what is, according to the SCCS, the maximum concentration considered safe for use of Silver Zinc Zeolite as a preservative in cosmetic products?*

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3. *Does the SCCS have any further scientific concerns with regard to the use of Silver Zinc Zeolite in cosmetic products?*

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5. MINORITY OPINION

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6. REFERENCES

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7. GLOSSARY OF TERMS

See SCCS/1647/23, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158

8. LIST OF ABBREVIATIONS

See SCCS/1647/23, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158