



Scientific Committee on Consumer Safety

SCCS

OPINION ON Colloidal Silver (nano)



The SCCS adopted this Opinion
at its plenary meeting on 24-25 October 2018

ACKNOWLEDGMENTS

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http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

This Opinion has been subject to a commenting period of 8 weeks after its initial publication (from 20 March until 15 May 2018). Comments received during this time were considered by the SCCS. Based on those comments, adaptations are made in the Chemical and Physical Specifications section as well as in the Reference section.

1. ABSTRACT

The SCCS concludes the following:

1. *In view of above, and taken into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Colloidal Silver when used in cosmetics including toothpastes and skin care products with a maximum concentration limit of 1%, taking into account the reasonably foreseeable exposure conditions.*

Only a limited amount of data was provided by the Applicants that corresponded to the SCCS Guidance on Safety Assessment of Nanomaterials in Cosmetics (SCCS 1484/12). The provided data were also not in line with the SCCS Memorandum on Relevance, Adequacy and Quality of Data in Safety Dossiers on Nanomaterials (SCCS/1524/13). Although other information is available in open literature relating to the toxicity of nano silver, their relevance with respect to the materials of this submission has not been considered by the Applicants. Due to a number of major data gaps, the SCCS is not in the position to draw a conclusion on the safety of colloidal silver in nano form when used in oral and dermal cosmetic products.

2. *SCCS is requested to address any further scientific concerns with regard to the use of Colloidal Silver in nano form in cosmetic products.*

In addition to safety assessment of colloidal silver in nano form, consideration should also be given to the likely presence of ionic silver in different type of final products.

Keywords: SCCS, scientific opinion, colloidal silver (nano), CAS 7440-22-4, EC 231-131-3, Regulation 1223/2009

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Colloidal Silver, 24+25 October 2018, SCCS/1596/2018

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Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

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

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning all types of 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

Article 2(1)(k) of Regulation (EC) No 1223/2009 establishes that "nanomaterial" means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

That definition covers only materials in the nano-scale that are intentionally made and are insoluble/partially-soluble or biopersistent (e.g. metals, metal oxides, carbon materials, etc.): it does not cover those that are soluble or degradable/non-persistent in biological systems (e.g. liposomes, emulsions, etc.). Article 16 of the Cosmetics Regulation requires the manufacturer to notify the Commission of any cosmetic product containing nanomaterials six months prior to being placed on the market, and Article 19 requires nano ingredients to be labelled (name of the ingredient, followed by 'nano' in brackets). If there are concerns over the safety of a nanomaterial, the Commission shall refer it to the Scientific Committee on Consumer Safety (SCCS) for a full risk assessment.

The Commission received 63 notifications of cosmetic products containing Colloidal Silver (CAS No 7440-22-4, EC No 231-131-3) in nano form, as reported in the attached list. This ingredient is reported in the CosIng database without any reference to the nano form with the function of abrasive, bulking and emulsion stabilising, but it is not regulated in Cosmetic Regulation (EC) No 1223/2009. According to the Applicants, the ingredient is used in nano uncoated form both in leave-on and rinse-off oral cosmetics products including toothpastes and skin care products with a maximum reported concentration limit of 1% and specifications as reported in the list attached to the mandate.

The Commission has concerns over the safety of the use of Colloidal Silver in nano form in cosmetic products.

The Commission published a 12-week call for data with the deadline of 30 June 2015, in which interested parties were invited to submit any relevant scientific information on the safety of Colloidal Silver (CAS No 7440-22-4, EC No 231-131-3) in nano form used in cosmetic products and in particular data regarding all toxicological end-points and an indication on the suggested concentration safe limits for this ingredient. The documentation received by Commission is annexed to the mandate.

Therefore, the Commission is requesting the SCCS to produce a safety assessment of the nano form of Colloidal Silver covered in the notifications listed in the annex to this mandate, in the above-mentioned categories of products, taking into account the reasonably foreseeable exposure conditions.

Terms of reference

- 1. In view of the above, and taking into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Colloidal Silver when used in cosmetics including toothpastes and skin care products with a maximum concentration limit of 1%, taking into account the reasonably foreseeable exposure conditions.*
- 2. SCCS is requested to address any further scientific concerns with regard to the use of Colloidal Silver in nano form in cosmetic products.*

3. OPINION

Preamble:

Initial assessment of all data submitted showed that the provided data by the Applicants appeared to be very minimal. No complete dossiers for all colloidal silver dispersions were submitted and there were hardly any data on physical chemical characterisation and experimental toxicity studies. Clarification on a number of aspects and missing safety data were needed before the SCCS could form an Opinion on the safety of the material.

To facilitate the evaluation process, the Applicants were asked to provide additional data, revise the information submitted in the dossier, and provide clarifications.

In response, some Applicants provided additional data and information. Much of this information related to antimicrobial activity of nano silver, which was not relevant to this evaluation. All the relevant information on colloidal silver dispersions, including additional data, has been described and assessed in the current Opinion.

In addition, the Commission gave out a Call for information in regard to the safety of the nano silver. The information received from various sources has also been considered in this Opinion.

3.1. CHEMICAL AND PHYSICAL SPECIFICATIONS

An overview on data on material characterisation is provided in the Table 1 of the Annex.

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Colloidal silver

3.1.1.2. Chemical names

Colloidal silver
Silver particles suspended in liquid
Non-ionic silver

SCCS comment:

The term colloidal silver implies that particles are in aqueous suspension. However, some proportion will also be in the form of ionic silver. Information is needed on the proportion of colloidal particles and ionic silver in a typical material.

3.1.1.3. Trade names and abbreviations

Silver Water nano-TECH/ aXonnite silver (A, B, C, D, J, K, L)
Premium Heritage Colloidal Silver (E)
Nanosrebro (F, G)
Nanocolloidal Silver (H₂O Ag) Non-Chemical (H)
Ag100 Koloidne Striebro (colloidal silver Ag 100) (I)

In the following Table, the trade names of colloidal silver dispersions from different manufacturers are described.

Table 1: Trade names of the various colloidal silver dispersions (manufacturers' names have been coded by the SCCS)

Nr.	Name of colloidal silver dispersion	CPNP code	References
A	Silver Water nano-TECH	35406	Ref* 1,2,3,37,39,40,41,43,48,55
B	Silver Water nano-TECH	195	Ref 4,5,6
C	Silver Water nano-TECH	201	Ref 7,8,9
D	Silver Water nano-TECH	100234	Ref 10,11,12
E	Colloidal Silver (Premium Heritage Colloidal Silver)	57700	Ref**13,14,15
F	Nanosrebro	35015	Ref 16,17,18
G	Nanosrebro	75612	Ref 19,20,21
H	Nanocolloidal Silver (H ₂ O Ag) Non-Chemical	71309	Ref ***22,23,24
I	Ag 100 Koloidné striebro	32936	Ref 25,26,27,50,51,52,53,54
J	Silver Water nano-TECH	1000800	Ref 1,2,3,37,39,40,41,43,48,55
K	Silver Water nano-TECH		Ref 1,2,3,37,39,40,41,43,48,55
L	Silver Water nano-TECH		Ref 1,2,3,37,39,40,41,43,48,55

* NB. The Silver Water nano-TECH seems to be the same product reported by 7 different Applicants. Therefore, there is overlap in the following references, but not all. They have different numbers in the CPNP portal but are the same: Ref 1, 4, 7, 10 and 43; Ref 3, 5, 11, and 48; Ref 6, 9 and 12; Ref 2 and 40.

** For this product, ref 13 and 15 are the same

*** For this product, ref 22 and 24 are the same

In the original dossier, nine Applicants provided data on five different colloidal silver dispersions (see Table 1). For every colloidal silver dispersion, three different files had been submitted; a safety file, a specification file and a file on the toxicity profile.

Three additional Applicants sent information on the Silver Water nano-TECH dispersion (J, K, and L) at a later stage. However, the information provided by the new Applicants was similar to the information already received. Three Applicants provided additional information on dispersions A, I and J.

3.1.1.4. CAS / EC number

CAS: 7440-22-4

EC: 231-131-3

INCI: CI 77820

3.1.1.5. Structural formula

Ag
Ag⁰ H₂O
H₂O Ag

Ref.: 13, 15, 22

3.1.1.6. Empirical formula

Ag
Ag⁰ H₂O

3.1.2. Physical form

Colloidal silver is described as water dispersion (colloid) of silver nanoparticles; it is a clear liquid with no odour. The following product specifications of the various forms of colloidal silver have been reported (Table 2):

Table 2: Product specifications as provided by the Applicants

Dispersions	Concentration	Particle size (% of the total amount)	Surface Area	Surface charge (Zeta potential)	REFs
A B D J K L	100±10 ppm (mg/kg)	3-5 nm (80-85%) 5-100nm(15-20%)	1 m ² /g (BET) 1 m ² /cm ³ (VSSA)		1,3,4, 5,7,10, 11,43, 48,55
C	50 ppm (mg/kg)	2-5 nm (70-75%) 5-100nm(25-30%)			8
E					
F G	1000 ppm	Lowest cut-off 1.56 nm Number weighted median 5.79 nm	192 m ² /g (BET)	50 mV	16,17
H	max 0.015 % silver				22
I		39 nm		-41.6 (± 10) mV	25,55

*Colloidal silver dispersions A, B, C, D, J, K, L are the same dispersions submitted by seven different Applicants. Also dispersions F and G seem to be similar (same name and specifications).

SCCS comment:

Information on concentration in terms of both particle mass and particle number per volume must be provided for dispersions and per mass for dry powders. The content of ionic silver should also be provided for each material when dispersed in aqueous media.

The data provided for surface area and VSSA for dispersions A, B, C, D, J, K and L do not seem to be correct. The large differences in surface charge for dispersions F, G and I need to be explained.

3.1.3. Molecular weight

Molecular weight of silver: 107.87 g/moles

Ref.:13, 15

3.1.4. Purity, composition and substance codes

Products are described as water dispersion (colloid) of silver nanoparticles with a concentration of (see also Table 2):

50 or 100 ppm (A, B, C, D, J, K, L)

Ref.: 1, 4, 7, 10, 43

1000 ppm (F,G)

Ref.: 16

0.015% (H)

Ref.: 22

Additional information

The total concentration of colloidal silver Ag 100 (material I) was determined by Atomic absorption spectroscopy (AAS) and was found to be 35.3 µg/ml (ppm). The ionic silver concentration in colloidal silver Ag 100 was determined by a total dissolved solids (TDS) meter and was found to be 28.2 µg/ml (ppm). The concentration of colloidal silver nanoparticles was determined to be $35.3 - 28.2 = 7.1$ µg/ml (7.1 mg/l = 0.0071 g/l). The number of moles (colloidal silver per volume) = 3.96×10^{19} moles/l.

Ref.: 53

SCCS comment:

Purity and composition data were provided for all but one (E) colloidal silver dispersions. Additional, more detailed information has been submitted for dispersion I. These data are, however, required for all colloidal silver dispersions.

3.1.5. Impurities / accompanying contaminants

According to the relevant Applicants, traces of heavy metals were quantified by a testing laboratory with satisfactory results (colloidal silver dispersion H, ref 22) and impurities endangering human health were not identified (colloidal silver dispersion I, ref 25).

Ref.: 22, 25

Silver dispersions A, B, C, and D have been indicated by the Applicants to be Ag4N. Furthermore, it is stated that dispersion A has "a very high chemical purity".

Ref.: 3, 5, 11

For one of the colloidal silver dispersions (dispersion E), an analysis of constituents has been performed (see Table 3).

Table 3: Analysis of colloidal silver dispersion (dispersion E)

Method reference	Test	Test description	Result	Units
M_ICP-OES	PHOSPHTO_2		<0.070	mg/l
M_ICPMS	ALUMINTO_2	Aluminium	0.021	mg/l
C_COLOUR	AMMONIA	Ammonia	<0.03	mg/l as N
M_ICPMS	ARSENITO_2	Arsenic	<1.000	ug/l
M_ICPMS	CADMIUTO_2	Cadmium	<1.50	ug/l
M_ICPMS	CALCIUTO_2	Calcium	0.37	mg/l
C_COLOUR	CHLORIDE	Chloride	<0.60	mg/l
C_COND	COND_20C	Conductivity	19	uS/cm
M_ICPMS	COPPERTO_2	Copper	<5.50	ug/l
C_ISE	F	Fluoride	<0.02	mg/l

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M_ICPMS	IRONDI_2	Iron (Dissolved)	<0.018	mg/l
M_ICPMS	IRONTO_2	Iron	<0.018	mg/l
M_ICPMS	LEADTO_2	Lead	<5.00	ug/l
M_ICPMS	MAGNESTO_2	Magnesium	<0.200	mg/l
M_ICPMS	MANGANTO_2	Manganese	<0.004	mg/l
C_COLOUR	NITRATE_N	Nitrate	1.220	mg/l as N
C_COLOUR	NITRITE_N	Nitrite	0.038	mg/l as N
C_PHY	ODOUR_DN	Odour (Quantitative)	0	DiIn. No.
C_ISE	PH	pH	8.46	pH Units
M_ICPMS	POTASSTO_2	Potassium	<0.750	mg/l
M_ICPMS	SILVERTO_2	Silver	14000.00	ug/l
M_ICPMS	SODIUMTO_2	Sodium	<2.500	mg/l
C_GRAV	SS_105	Solids (Suspended at 105C)	1.0	mg/l
C_COLOUR	SULPHATE	Sulphate	0.84	mg/l
C_GRAV	TDS_180	Solids (Total Dissolved at 180C)	<0.00	mg/l
M_ICPMS	TOT_HARD	Hardness (Total)	0.97	mg/l as CaCO ₃
C_NEPH	TURBIDITY	Turbidity	1.12	FTU
M_ICPMS	ZINCTO_2	Zinc	10	ug/l

Ref.: 14

Additional information

For colloidal silver dispersion I, detailed information on purity has been submitted. Purity has been analysed using two different methods, i.e. using an EDX (Energy Dispersive X-ray) analyser or by FTIR (Fourier Transform Infrared) spectroscopy. The dispersion contains only silver particles, no other elements have been found. Furthermore, addition of organic compounds has been excluded.

Ref.: 50

SCCS comment:

According to SCCS 1484/12, information on full chemical composition of each nanomaterial must be provided. For dispersion (E), detailed information on constituents was provided. Additional information on dispersion I was provided in a later stage. However, similar data should be provided for all colloidal silver dispersions under consideration. This should include purity (total silver and any impurities), concentration (colloidal particles in ppm and ionic silver in ppm), any coatings or surface modifications, any doping materials, whether or not the particles were encapsulated, and any dispersing agents, or other additives/formulants e.g. stabilisers used.

Global statements such as "traces of heavy metals were quantified by a testing laboratory with satisfactory results" and "impurities endangering the human health are not identified" should be supported by data.

Ag4N (dispersions A, B, C and D) describes the quality of silver in terms of limits of various metallic and non-metallic impurities (<http://www.espimetals.com/index.php/online-catalog/439-Silver>).

3.1.6. Solubility

Seven Applicants stated that solubility in water is unlimited (A, B, C, D, J, K, L).

Ref.: 1, 4, 7, 10

Additional information

Additional information for these dispersions is that the solubility is below 0.01 mg/l.

Ref.:55

For dispersion I, additional data on solubility have been provided. The concentration of ionic silver in as-prepared colloidal silver Ag 100 by TDS was measured every 24 hours (for several months). No increase in ionic silver concentration was demonstrated, which allows the manufacturer to consider that colloidal silver Ag 100 is a stable suspension. No "further dissolution" of silver, i.e. $Ag_0 \rightarrow AgI$ in aqueous solution occurs.

Ref.: 53

SCCS comment:

Information on dissolution rates of the nanomaterial in relevant solvents must be provided for all colloidal silver dispersions. Global statements about solubility not supported by data cannot be accepted.

For colloidal silver dispersion A, B, C, D, J, K, L, no experimental data on solubility were submitted. Additional experiments on solubility were only provided for dispersion I. Similarly, the statement "no further dissolution of silver occurs" is not supported by the data provided.

3.1.7. Partition coefficient (Log P_{ow})Log P_{ow}: not applicable**3.1.8. Additional physical and chemical specifications**

Table 4: Additional physical and chemical specifications provided by ten Applicants

Specification	A, B, C, D, J, K, L Ref 5,11,39,42,46	E Ref 13,15	H Ref 22	I Ref 52	Comments column I
Melting point		960 °C			
Boiling point	Approx. 100 °C	2212 °C		99.5 °C	Determined by thermometer using scale up to 110 °C
Density	0.99-1.01 g/cm ³ 1.00 kg/l (at 20.0 °C)			0.997504 g/cm ³ at 24.0 °C	Determined by a pycnometer Precision level of density in column I is too high
Viscosity	1000 x 10 ⁻⁶ Pa x s (100 ppm)				
pH	5-7 (6-7.5) (100 ppm)		5.5 – 7 (max 0.015%)	7.33 (at 23.1 °C)	Provided by standard laboratory pH meter
Conductivity	5.0-50.0 µS/cm 23.07 µS			0.5 µS	Tested by conductometer
Turbidity/Opacity	max 8 NTU				
Colour	max 5 Pt/l				

NB. Only real data provided by the Applicant are mentioned in the Table, statements such as “not provided”, “does not concern” etc. are not included as they give no relevant information for the Opinion.

SCCS comment:

Data should be provided for the silver nanomaterial in the colloidal silver dispersion and not for the dispersion itself. The boiling point of approx. 100 °C or 99.5 °C (column 2 and 5 of Table 4) is the boiling temperature of the dispersion’s water content.

Additional physicochemical characterisation data should be provided for all the different colloidal silver dispersions.

3.1.9. Particle size and shape

Dispersion A, B, C, D, J, K, L: 2-5 nm (80-85%) 5-100 nm (15-20%)

Ref: 3, 5, 11, 39, 48

Dispersion F, G: Lowest cut-off = 1.56 nm
 Number weighted median = 5.79 nm

Ref: 16, 19

Dispersion I: 39 nm

Ref: 25

A microscopic picture (scanning electron microscopy, SEM) was only provided for colloidal dispersion I.

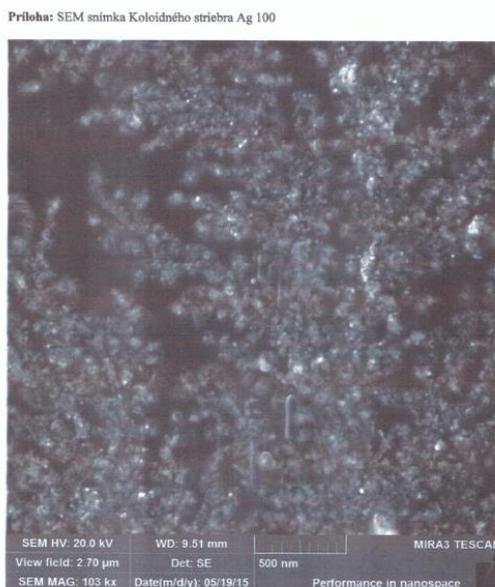


Figure 1. SEM picture of dispersion I

Ref.:26

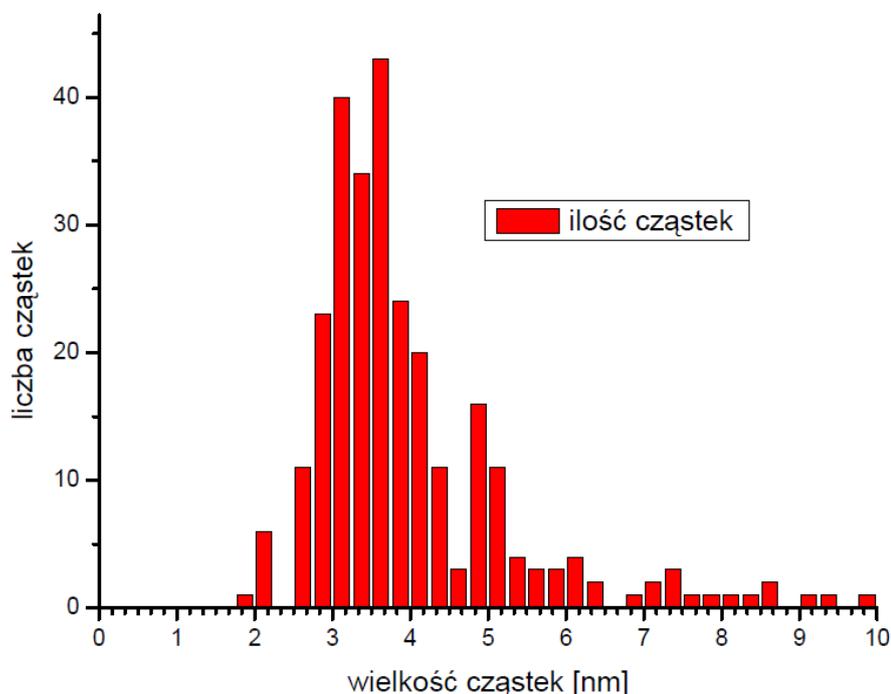
Additional information

The physical form/shape of the nanoparticle of material A is stated to be spherical.

Ref.: 39

Particle size distribution of colloidal silver dispersion A has been determined by means of a JEM 2000EX Transmission Electron Microscopy (TEM) with beam energy of 200 keV and a resolution of 0.3 nm. The microscopic images were taken to determine particle morphology. The particles deposited on the carbon film were single and in clusters. Diameters of the

individual particles were measured and the results were presented in the form of a histogram showing the number of particles of a given diameter. Images were recorded on a photographic film, which after the processing was scanned with the Nikon Super Colorscan 8000. Results of the particle size distribution are depicted in Figure 2.



Note:
wielkość cząstek = particle size
liczba cząstek or ilość cząstek = number of particles

Figure 2: Particle size distribution of Silver Water nano-Tech

Diffraction images were used to determine the internal structure. In the case of individual particles, the diffractograms obtained showed wall-centered structures of the lattice constant $a = 0.401 \pm 0.08$ nm. Electron diffraction from the area where the particles were present in the clusters showed the presence of orientation order, showing the intensity enhancement of the diffraction rings at 60° .

Ref.: 2, 40

In addition, a detailed report on TEM analysis of dispersion A has been provided. TEM analysis showed that nanocrystalline silver particles are present in the test fluid, with an average diameter of 3.5 nm as well as larger particles of several microns in diameter.

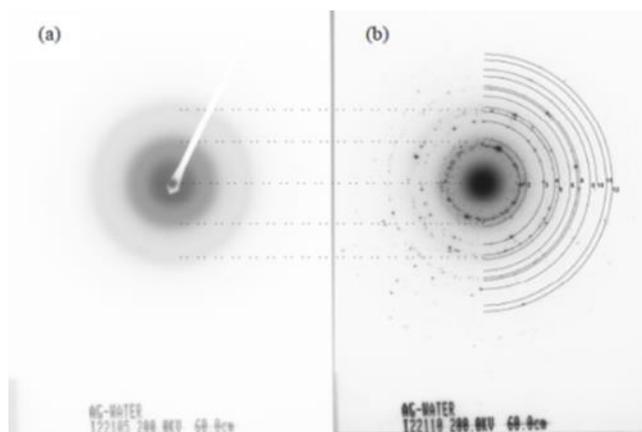


Figure 3: Diffraction images from areas containing particles of dimensions: (a) nanometric, (b) micrometric.

The particles of both sizes have a crystal structure with a face-centered cubic structure with the lattice constant of $a = 0.408 \pm 0.002$ nm. In the case of nanoscale particles, no rare structural defects, such as twinning, have been observed. Examples of nanoparticles observed on two different filters are depicted in Figure 4.

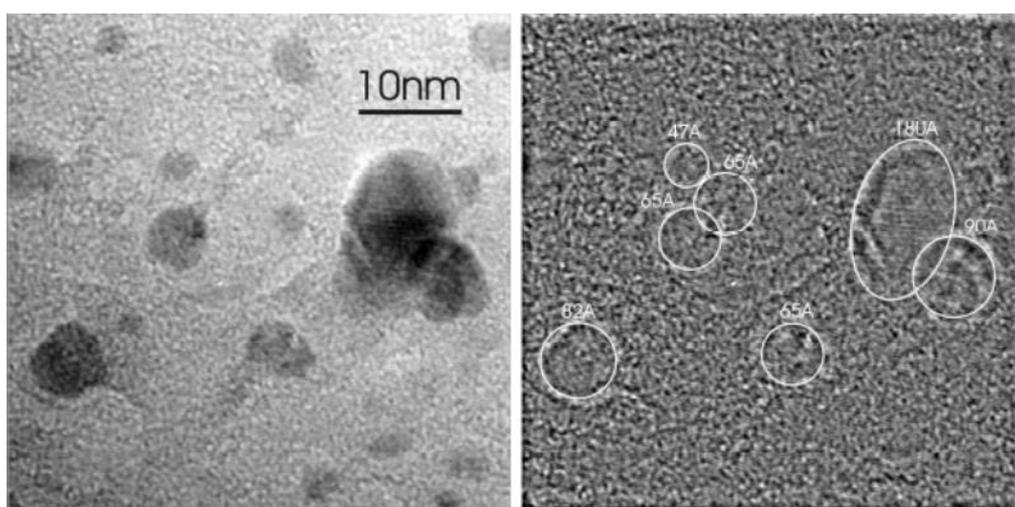


Figure 4: High resolution image showing the same fragment of nanosilver particles on amorphous carbon film (left) and subjected to Fourier filtration (right)

Ref.: 44

SCCS comment

For all silver nano particles in this submission, an appropriate characterisation should be provided.

Information on primary and secondary particle size, particle number size distribution and particle mass size distribution must be provided for each material. For this, the use of more than one analytical method (one being electron microscopy based imaging) for determination of size parameters has been recommended in SCCS 1484/12.

Information on the physical form and crystalline phase/shape must be provided. The information should indicate the shape and aspect ratio of the nanomaterial and whether the nanomaterial is in the form of primary particulates or agglomerates/aggregates.

In the additional information provided for colloidal silver dispersion A, the SCCS has observed some inaccuracies.

Firstly, there are two different numbers mentioned for the same dispersion A in the diffraction pattern for the lattice constant a ($a = 0.401 \pm 0.08$ nm in Ref. 2 and 40 and $a = 0.408 \pm 0.002$ nm in Ref. 44, respectively). This may mean that the arrangement of atoms within the lattice is different.

Secondly, Figure 3 and 4 in this Opinion are of poor quality and difficult to interpret. They seem to be not representative of the size distribution as mainly larger structures are shown. More in detail, the selected area diffraction pattern from Figure 3a (Figure 1a in Ref. 44) is not a selected area diffraction (SAD) pattern corresponding to a crystalline phase but rather to an amorphous one. There is no additional information on this aspect. Furthermore, the SAD pattern from Figure 3b (Figure 1b in Ref. 44) corresponds to a nanostructure phase (not a micrometric one). Continuous rings, as presented, are not representative for micrometric entities.

Also, it is mentioned in Ref. 44 that a microscopic image is prepared using dark field mode from electrons forming the first diffraction ring (ring number 1 in Fig. 3a of this Opinion, Fig 1a in Ref. 44), but the SCCS is of the opinion that the image is not a dark field one. In a dark field image, the background is black and the diffracted area is bright. In the image mentioned there is an area with no materials, and this should be black. Therefore, the SCCS concludes that this is not a dark field image but a bright field one.

In spite of the fact that some detailed additional information for colloidal silver dispersion A has been provided, the information is still not sufficient for a proper characterisation of all the colloidal silver dispersions.

3.1.10. Crystal structure

SCCS Comment

Although some of the Applicants have stated that the crystalline form of the material is spherical-crystalline, no supporting evidence has been provided. It is unclear to the SCCS how the Applicants arrived at the stated conclusions.

Furthermore, the images provided in the additional information for colloidal silver dispersion A (Ref. 44) indicate, apart from being crystalline, also an amorphous form (see Figure 3b of this Opinion). However, no detailed information is provided on this aspect.

3.1.11. UV absorption

Additional data on UV and visible absorption have been submitted for colloidal silver dispersion I. The UV/Vis absorption spectrum of dispersion I is depicted in Figure 3. This Figure shows that the UV/Vis spectrum of colloidal silver Ag 100 did not show any significant absorption peaks over 250 nm.

Ref.: 54

SCCS comment:

Although the UV/Vis absorption spectrum now has been provided for one of the colloidal silver dispersions, data have not been submitted for any of the other materials and should be provided.

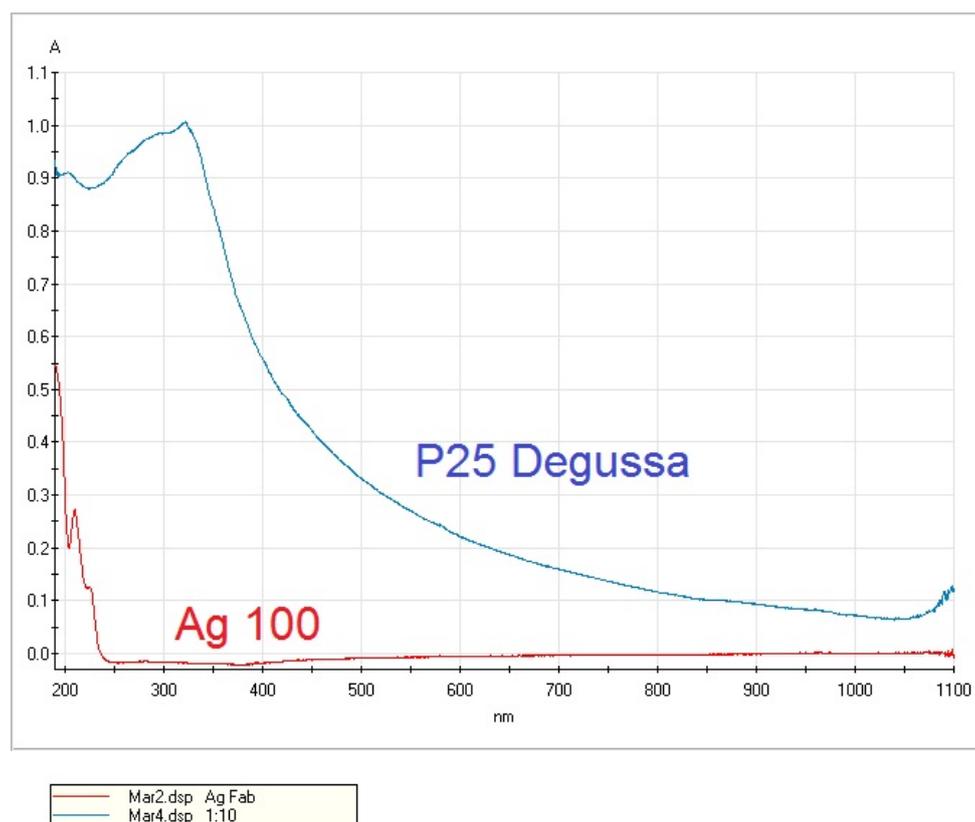


Figure 5: UV/Vis absorption spectrum of colloidal silver Ag 100 (dispersion I) (red). For comparison, the absorption spectrum of typical photocatalyst, P25 Degussa (with the same concentration of TiO₂ as colloidal silver Ag 100, i.e. 35 ppm) is also shown (blue).

3.1.12. Surface characteristics

Information on BET (Brunauer Emmett and Teller method) for the specific surface area measurement is only provided for colloidal silver dispersion G. For dispersion A, additional information has been provided both on the BET specific surface area as well as on the volume specific surface area (VSSA). For all other colloidal silver dispersions, this information is not provided. For all materials it was mentioned that they are uncoated materials.

SCCS comment:

Detailed information on nanomaterial surface characteristics must be provided. Information on the BET specific surface area of the nanomaterial and VSSA must be provided for each material (see Kreyling *et al.*, 2010 and Wohlleben *et al.*, 2017 for calculation of VSSA). It is noted that the BET-surface area can only be provided for the source material in powder form.

Ref.: 38, 67

3.1.13. Droplet size in formulations

No data provided.

SCCS comment:

Inhalation exposure is not expected during the use of the submitted products, so information on droplet size is not relevant.

3.1.14. Homogeneity and stability

The Applicants did not provide data on homogeneity and stability of the nanomaterial in relevant formulation (colloidal silver dispersions). Rather, they stated that the cosmetic product is stable in prescribed conditions of application or at usual storage conditions and for foreseeable usage until the declared expiry period.

Ref.: 1, 2 (4, 5, 7, 8, 10, 11), 25, 26, 43

Additional information

Under normal conditions of use and storage, colloidal silver dispersion A is stable (and shows no reactivity).

Ref.: 40

SCCS comment:

The Applicants did not provide any data. Data on stability/dissociation constant of the nanomaterial in relevant formulation/media must be provided for all colloidal silver dispersions.

3.1.15. Other parameters of characterisation*Additional information*

The photocatalytic activity of colloidal silver dispersion I has been studied by degradation of methylene blue under sunlight irradiation measured by UV/VIS. It was concluded from the measurements that dispersion I does not exhibit photocatalytic activity.

Ref.: 51

SCCS comment:

Data on photo-catalytic activity should be provided for all applications intended for use on the skin.

3.1.16. Summary on supplementary physicochemical characterisation**SCCS comments to physicochemical characterisation**

Overall, the information provided on the physicochemical characterisation of the colloidal silver suspensions is minimal and patchy.

The physicochemical characterisation of the colloidal silver dispersions under evaluation is insufficient for assessment of its dermal and oral applications. According to the SCCS Guidance on the safety assessment of nanomaterials in cosmetics (SCCS 1484/12), the following information on the physicochemical characteristics of colloidal silver should be provided:

- Information on concentration in terms of particle mass (dry powder) and particle number per volume (dispersions) for all colloidal silver dispersions
- Content of ionic silver for each material when dispersed in aqueous media
- Full chemical composition of the nanomaterial including purity (total silver, any impurities) and concentration (colloidal particles in ppm and ionic silver in ppm),

surface moieties, doping material, or encapsulating materials, and dispersing agents, other additives or formulants, e.g. stabilisers used in the formulation

- Data on solubility and dissolution rates of the nanomaterial in relevant solvents
- Additional information on physicochemical characterisation, such as melting and boiling temperature (for the silver nanomaterial in the dispersion), density, viscosity of liquid dispersions, pH, conductivity, turbidity and colour
- UV absorption (extinction coefficient), light reflection of typical suspensions
- Information on redox potential, including documentation of the conditions under which the redox potential was measured
- For all materials, information on primary and secondary particle size, particle number size distribution and particle mass size distribution
- For this, it is recommended to document the measurement method for determining size, and to use more than one method (one being electron microscopy based imaging) for determination of size parameters
- Data on the physical form and crystalline phase/shape. The information should indicate whether the nanomaterial is present in a particle-, tube-, rod- shape, crystal or amorphous form and also whether the nanomaterial is in the form of primary particulates or agglomerates/ aggregates
- Detailed information on the nanomaterial surface characteristics for all of the colloidal silver dispersions. This should include information on surface charge (zeta potential), morphology/topography, interfacial tension, reactive sites (if any), as well as any chemical/ biochemical modifications that could change the surface reactivity or add a new functionality
- Information on the BET specific surface area of the nanomaterial and the volume specific surface area (VSSA) for all materials (see Kreyling *et al.*, 2010 for calculation of VSSA)
- Data on stability/dissociation constant of the nanomaterial in relevant formulation/ media
- Data on photo-catalytic activity for applications intended for use on the skin exposed to sunlight
- Product specifications and any batch-to-batch variation during manufacturing

In spite of the fact that additional data have been provided for some colloidal silver dispersions, SCCS is of the opinion that it is still insufficient for a proper characterisation of all colloidal silver dispersions submitted in the current dossier.

Appropriate characterisation should be provided for the colloidal silver dispersions in nano form in this submission.

3.2. FUNCTION AND USES

Colloidal silver is intended to be used as an antimicrobial agent in cosmetics including toothpastes and skin care products with a maximum concentration limit of 1%. The majority of the colloidal silver dispersions in this submission (all but one) are used in skin care products.

Examples of skin care products are face creams, body creams, cleansing products, shampoos and body masks. Only one of the colloidal silver dispersions is intended to be applied in oral products like toothpaste (See also Table 5 below).

Table 5: Description of the function and uses of the Colloidal silver dispersions

Manufacturer	Cosmetic products the colloidal silver is used in	Foreseeable exposure conditions
A, B, C, D, J, K, L	Face care products, eye contour products, cleansing products, face mask, body care products	Dermal route, leave-on
E	Toothpaste	Oral route

F	Soap products, shampoo, bath/shower products, products with anti-perspirant activity	Dermal route, rinse-off
G	Face care products other than face mask	Dermal route
H	Body care products	Dermal route
I	Other skin care products	Dermal route

Ref.: 55, 57, 58, 60

3.3. TOXICOLOGICAL EVALUATION

An overview of the toxicological studies provided is described in the Table 2A and 2B of the Annex.

3.3.1. Acute toxicity

3.3.1.1. Acute oral toxicity

The oral LD50 (rats, guinea pigs) of (colloidal) silver is > 5000 mg/kg (material A, B, C, D, J, K, L)

Ref.: 1, 4, 7, 10, 13, 15, 22, 43

OECD test guidelines (TG) 420, LD50 (rat) >2000 mg/kg, no symptoms of toxicity (material F, G)

Ref.: 18, 19

Oral LD50 (mice) of (colloidal) silver is > 10000 mg/kg (material H)

Ref.: 22

Oral LD50 for mice is 100 mg/kg (material F)

Ref.: 18

SCCS comment:

Although some statements have been given on the oral toxicity of colloidal silver, no original study reports have been provided. No information on material characterisation for the materials used in the studies has been given. It is not clear whether (and if so in which respect) the material used in the acute oral toxicity studies corresponds to the materials in this submission. Proper assessment of the acute oral toxicity relevant to the materials under consideration should be provided (see SCCS 1564/15 and SCCS 1524/13).

Based on the information provided by the Applicants, no conclusion can be drawn on acute oral toxicity.

3.3.1.2. Acute dermal toxicity

OECD 402, LD50 >2000 mg/kg, no symptoms of toxicity (material G)

Ref.: 19

SCCS comment:

No original study report has been provided. It is not clear whether the study adhered to a GLP or an OECD test guideline (TG). No information on material characterisation for the material used in the study has been given. It is not clear whether (and if so in which respect) the material used in the acute dermal toxicity study corresponds to the materials of this submission. Proper assessment of the acute dermal toxicity relevant to the materials under consideration should be provided (see SCCS 1564/15 and SCCS 1524/13). Based on the information provided, no conclusion can be drawn on acute dermal toxicity.

3.3.1.3. Acute inhalation toxicity

No data provided.

SCCS comment:

As the Applicants intend to use colloidal silver only for dermal and oral applications, information on this endpoint is not required.

3.3.2. Irritation and corrosivity**3.3.2.1. Skin irritation**

Five references (1, 4, 7, 10, 50; corresponding to colloidal silver dispersion A, B, C, D, J, K, and L) state that the material does not exert specific irritation. Two further references (13, 15, colloidal silver dispersion E) state that there are no data available. One reference (19, colloidal silver dispersion G) mentions results from OECD TG 404, i.e. an Irritation index (PII=0,34), classified as "neglectable". One reference (18, colloidal silver dispersion F) states there is no effect on skin irritation (rabbit, 0,5 g/ 5 ml H₂O for 4h).

SCCS comment:

Information on skin irritation should be provided for dermally-applied cosmetic products (see SCCS 1484/12 and SCCS 1564/15). With respect to the OECD TG 404 study mentioned by ref 19, no original study report has been provided. No information on the material characterisation for the material used in the study has been given. It is not clear whether (and if so in which respect) the material used in the skin irritation study corresponds to the materials in this submission. Guideline compliance is unclear.

Therefore, no conclusion can be drawn on skin irritation based on the information submitted.

3.3.2.2. Mucous membrane irritation / Eye irritation

Five references (1, 4, 7, 10, 43; corresponding to colloidal silver dispersion A, B, C, D, J, K, and L) state that irritation of eye can result from extended contact. Two references (18, 19, colloidal silver dispersion F, G) state there is no irritating potential on eyes. One of them is based on OECD TG 405 (19, colloidal silver dispersion G), the other on a study using 180 mg of nanosilver in rabbits (18, colloidal silver dispersion F). One Reference (22, colloidal silver dispersion H) mentions the possibility of eye irritation and two references (13, 15, colloidal silver dispersion E) state that there are no data available.

SCCS comment:

Information on mucous membrane/eye irritation should be provided for orally- (toothpaste) and dermally-applied cosmetic products (see SCCS 1484/12 and SCCS 1564/15). With respect to the OECD TG 404 study mentioned by ref 19, the SCCS notes that no original study report has been provided. No information on material characterisation for the material used in the study has been given. It is not clear whether (and if so in which respect) the material used in the skin irritation study corresponds to the materials in this submission. Guideline compliance is unclear.

Therefore, based on the information provided, no conclusions can be drawn with respect to mucous membrane irritation/ eye irritation.

3.3.2.3. Airways irritation

No data available.

SCCS comment:

As the Applicants intend to use colloidal silver only for dermal and oral applications, information on this endpoint is not required.

3.3.3. Skin sensitisation

Five references (1, 4, 7, 10, 13, 15, 18) state that the colloidal silver dispersions do not exert specific sensitisation potential and do not contain any of the 36 allergens. Furthermore, there are no data on respiratory sensitisation.

Ref.: 1, 4, 7, 10, 13, 15, 18

It is further stated that results of tests in volunteers with the finished product have shown no sensitisation or allergenicity. "The tests were performed with carefully selected volunteers, with the use of the dermatological patch test method according to the semi-open Declaration of Helsinki with the later subsequent additions, the EU and the Republic of Poland rules and the guidelines of the Cosmetic Europe".

Ref: 22

Additional information

Additional information has been provided and states that colloidal silver dispersion A does not induce skin sensitisation (without any experimental evidence).

Ref.: 42

SCCS comment:

Statements made by the Applicants have not been supported by data. No study data on skin sensitisation have been provided. The Applicants did not specify the 36 allergens that are apparently not present.

Adequate information on skin sensitisation on relevant materials should be present in a dossier of a cosmetic ingredient. No information on material characterisation for the material used in the study has been given.

Therefore no conclusion can be drawn with respect to skin sensitisation based on the information provided.

3.3.4. Absorption**3.3.4.1. Dermal / percutaneous absorption**

No data provided.

SCCS comment:

According to the SCCS Guidance on the safety assessment of nanomaterials in cosmetics, (SCCS 1484/12) a dermal percutaneous absorption study with the relevant colloidal silver dispersions including proper material characterisation should be provided in order to determine whether there is evidence for the systemic absorption of silver nanoparticles via the skin.

In vitro penetration data (preferably from own studies or relevant open literature) should be provided for all colloidal silver suspensions as part of the base set requirements for the assessment of cosmetic products (including proper material characterisation).

3.3.4.2. Absorption by the respiratory tract

No data provided

SCCS comment:

Uses leading to inhalation uptake are not claimed by the Applicants and therefore not considered by the SCCS in this Opinion.

3.3.4.3. Absorption by the oral route

No data provided.

SCCS comment:

Since the colloidal silver dispersion E is applied in toothpaste, information on oral absorption of this material should be provided including proper material characterisation.

3.3.5. Inhalation toxicity

No data provided

SCCS comment:

Uses leading to inhalation uptake are not claimed by the Applicant and therefore not considered by the SCCS in this Opinion.

3.3.6. Repeated dose toxicity

3.3.6.1. Repeated dose oral toxicity

No data provided.

3.3.6.2. Subchronic (90 days) toxicity (oral, dermal)

No data provided.

3.3.6.3. Chronic (>12 months) toxicity

No data provided.

SCCS comment on repeated-dose toxicity:

The Applicants should consider the likelihood of systemic exposure under foreseeable uses (considering oral as well as dermal uses). Information on repeated dose toxicity is necessary for the safety evaluation where the product use (e.g. as toothpaste or face care/body care products and shampoo) could lead to internal exposure of the consumer to silver nanoparticles. In case of considerable uptake, information on carcinogenicity and reproductive toxicity would also be necessary.

The SCCS is aware that information on repeated dose-toxicity for nano silver is available from the published literature. However, it is not clear how far the materials considered in these studies are representative for the materials of this submission in terms of characterisation.

3.3.7. Mutagenicity / Genotoxicity

One reference (18) states that no effect on genotoxicity has been shown, without describing any experimental results or study design. Furthermore, no data on mutagenicity/genotoxicity have been provided.

Ref.: 18

Additional information

Additional information has been provided for colloidal silver dispersion A, which states that the dispersion does not show mutagenic information on reproductive cells (without any experimental evidence).

Ref.: 42

Other additional information is provided for colloidal silver dispersion J. Both a cytotoxicity test *in vitro* (agar diffusion) and a genotoxicity test (micronucleus test) have been performed (Table 6).

Table 6: Design and summary of the results of the cytotoxicity and genotoxicity tests for colloidal silver dispersion J:

No.	Parameter	Test method	Requirement	Result
1.*	Cytotoxicity in vitro	agar diffusion acc. to PN-EN ISO 10993-5:2009	-	cytotoxicity grade – “0” interpretation – none cytotoxicity final result – sample non cytotoxic
2.	Genotoxicity	micronucleus test acc. to PN-EN ISO 10993-3:2014 PN-EN ISO 10993-12:2012	-	equivocal result

* method within the scope of accreditation no. AB 774

For both cytotoxicity and genotoxicity testing, the mouse fibroblasts cells NCTC clone 929 ATCC was tested. Detailed results of the genotoxicity study are presented in Table 7.

Table 7: Detailed results of the genotoxicity test (given as % of binucleated cells with micronuclei in population of binucleated cells):

Test without metabolic activation, short-term		
Cell culture control	Positive control	Tested sample
2,31% ± 0,86%	23,87% ± 3,82% (YES)	No result*
Test without metabolic activation, long-term		
Cell culture control	Positive control	Tested sample
2,81% ± 0,85%	82,74 ± 8,02% (YES)	No result*
Test with metabolic activation S9, short-term		
Cell culture control	Positive control	Tested sample
2,27% ± 0,99%	14,38% ± 1,45% (YES)	2,51% ± 0,50% (NO)

*Evaluation of genotoxicity was impossible due to the observed cytotoxic effect of the tested sample.

The conclusion from the study is that within the tested scope, the sample is non-genotoxic. Without metabolic activation, cytotoxicity of the tested sample has been observed.

Ref.: 59

SCCS comment:

The information provided in the additional study on cytotoxicity and genotoxicity is not acceptable, nor sufficient. The results of the whole study (on both cytotoxicity and genotoxicity testing) are not reliable for the following reasons:

SCCS comments on the cytotoxic study:

- According to the data provided, only one concentration of 50 ppm (50 µg/mL) was tested and no cytotoxicity was observed. However, from the information available in published literature, it is known that the EC50 for silver nanoparticles may vary and can be below 50 µg/mL, depending on cell types and particle sizes (Liu et al, 2010, Braydich-Stolle et al, 2005, Rosario et al, 2016, Park et al, 2011, Huk et al, 2014).
- No information on control substances used was given, neither positive nor negative.
- No data are provided on stability of the silver nanoparticle suspension and how it was applied on the agar.
- No information on number of replicates is given.
- The agar diffusion test used is not considered suitable to determine cytotoxic properties of silver nanoparticles. According to PN-EN ISO 10993-5:2009 ('8.4.1 Agar diffusion 8.4.1.1) the test allows only a qualitative assessment of cytotoxicity. Also, ISO 10993-5 is dedicated mainly to the testing of extracts of medical devices and not pure chemicals.
- More specifically for nanomaterials, ISO 19007 describes an *in-vitro* MTS assay for measuring cytotoxic effects of nanomaterials. Other quantitative assessments also might be used (such as the NRU cytotoxicity test; the colony formation cytotoxicity test; the MTT cytotoxicity test and the XTT cytotoxicity test) under the condition that assay interference is considered. The SCCS is therefore of the opinion that a method that is not prone to interference should be preferably used, such as colony-forming efficacy.
- The cytotoxicity test should be carried out at different concentrations to enable calculation of EC50 to compare the relative toxicity of the various colloidal silver dispersions in nano form.

Ref.: 61, 62, 63, 64, 65

SCCS comments on the genotoxicity study:

- It is not clear to the SCCS why an ISO guideline for testing medical devices was followed, while cosmetic ingredients should be tested using OECD TG test guidelines or EU methods (See SCCS 1484/12)
- L929 fibroblasts are not suggested in OECD TG 487: the choice of the cell line was not justified
- No data on positive control substances are given (concentrations, vehicles, etc.)
- No data have been provided which are necessary to demonstrate that the cells in culture have divided, so that a substantial proportion of the cells scored have undergone division during or following treatment with the test chemical. The measurement of Relative Population Doubling (RPD) or Relative Increase in Cell Count (RICC) is recommended to estimate the cytotoxic and cytostatic activity of a treatment – apparently no such parameters were assessed.
- In the study only one concentration has been evaluated (10 ppm). At least three test concentrations (not including the solvent and positive controls) that meet the acceptability criteria (appropriate cytotoxicity, number of cells, etc.) should be evaluated.
- A cytotoxic effect of the test item was observed after 6 or 30 h of exposure in the absence of S9-mix, but of unknown value. Due to this reason, further testing in the absence of S9-mix was not performed. No data on cell viability after exposure to the test item in the presence of S9-mix were provided. According to OECD TG 487, the highest concentration should aim to achieve $55 \pm 5\%$ cytotoxicity, using the recommended cytotoxicity parameters (which were not evaluated at all in the study).

Mutagenicity/genotoxicity data from *in vitro* studies would be required for all colloidal silver dispersions as part of the base set requirements for assessment of cosmetic products (including proper material characterisation). Any existing data from *in vivo* studies (conducted prior to 11 March 2013) with relevant, well-characterised materials should also be provided.

In a previous Opinion (SCCS/1577/16), the SCCS noted that mutagenicity/genotoxicity data on silver nanoparticles were inconclusive.

Ref.: 34

3.3.8. Carcinogenicity

One Applicant (reference 18) stated that there is no effect on carcinogenicity citing reports from the American Conference of Governmental Industrial Hygienists (ACGIH), the International Agency on Research on Cancer (IARC) and the National Toxicology Program (NTP). Another Applicant stated that carcinogenicity classification was not possible from current data. However, tumours at site of application were reported.

Ref.: 13, 15, 18

Additional data

Additional data on colloidal silver dispersion A state that carcinogenic effects have not been reported (without any underlying experimental data). Also, according to the Applicant of dispersion A, the product is not classified in the CMR categories 1A, 1B, and 2.

Ref.: 41, 42

SCCS comment:

No proper data or studies performed were provided. Incomplete citations to reports of the ACGIH, IARC and NTP were used, without stating the year of publication. This information should be provided. Furthermore, the Applicants did not substantiate the statements made ("Classification not possible from current data" and "Tumours at site of application") by sound data.

As described in the SCCS Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS 1484/12), if considerable systemic exposure or genotoxicity cannot be excluded, information on carcinogenicity is required.

The SCCS notes that no information has been provided on systemic availability via the relevant uptake route(s) or on genotoxicity that would allow drawing conclusions on the need for information on carcinogenicity.

3.3.9. Reproductive toxicity

No information was provided.

SCCS comment:

As described in the SCCS Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS 1484/12), if considerable systemic exposure cannot be excluded, information on reproductive toxicity is required.

The SCCS notes that no information has been provided on systemic availability via the relevant uptake route(s) that would allow drawing conclusions on reproductive toxicity.

3.3.10. Photo-induced toxicity

No information was provided.

SCCS comment:

Information should be provided for those products intended to be used on skin that is exposed to sunlight.

3.3.11. Toxicokinetics

No information was provided.

SCCS comment:

According to the SCCS Guidance on the safety assessment of nanomaterials in cosmetics (SCCS 1484/12), it is necessary to determine whether systemic absorption is possible via the relevant uptake pathway(s), in this particular case the oral and the dermal uptake route. Where tests on oral, inhalation or dermal/ percutaneous absorption show evidence for systemic absorption of nanoparticles, initial focus of toxicological investigations should be on determining Absorption, Distribution, Metabolism and Excretion (ADME) parameters to understand the fate and behaviour of nanoparticles in the body and to identify the likely target organs. The investigations should determine whether there are any changes in physicochemical characteristics of the nanoparticles, in terms of surface binding of proteins or other moieties that may have altered interaction with biological systems, and whether there are any changes in the integrity of the nanostructure, or agglomeration/ aggregation behaviour.

The SCCS is well aware that literature information on the toxicokinetics of nanosilver is insufficient (see SCENIHR, 2014). Nevertheless, efforts should be undertaken to address these issues based on available information and experimental studies (see also the section on dermal absorption).

Ref.: 28

3.3.12. Human data

Testing of the toxicological effects of the product was performed according to Colipa Guidelines on a group of volunteers. All participants fulfilled all the criteria for being assigned to the study, were clearly informed and gave their written consent before participation. The product was applied undiluted on the back of the volunteers repeatedly. All of the volunteers were visually controlled in periodical intervals after application. Volunteers subjectively commented product properties like unpleasant feelings, itching and burning on application area. Mild to moderate skin changes on the application area were reported, like redness, for example.

Ref.: 25

Additional data

Additional information states that colloidal silver dispersion A is not hazardous to human health (without any experimental data).

Ref.: 37

In addition, a dermatological assessment has been conducted in a contact patch semi-occlusive test testing a dispersion called demineralised water "PPUH PAWEŁ" with silver colloid Ag⁰ at a concentration of 10 ppm. Twenty volunteers (18 women, 2 men) were selected for the study, including 20 people with a positive allergic history. No allergic reaction was observed in the entire study group (including the persons with positive allergic interview), which indicates that the preparation did not exhibit irritating and sensitising properties.

Ref.: 49

SCCS comment:

The SCCS has considered that the information provided by the Applicants is insufficient. The Applicants are referred to consider the published scientific literature, which is abundantly available including the occupational exposure limits (OELs; Weldon et al, 2016).

Ref.: 35

3.4. EXPOSURE ASSESSMENT

An overview of data on the exposure assessment provided is described in the Table 3 of the Annex.

SCCS comment:

No proper exposure assessment according to the SCCS Notes of Guidance has been provided by the Applicants.

The Applicants are advised to consult the SCCS Notes of Guidance (http://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_190.pdf) for exposure assessment and calculation of the SED.

3.5. SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

Safety evaluation is not possible on the basis of the information provided by the Applicants or available from the other sources.

3.6. DISCUSSION

In addition to the information provided by the Applicants, a Call for Data was made by the European Commission. Information received as a result of this Call has also been considered by the SCCS. However, it was not possible to relate toxicological data from this information with the type of materials considered in this assessment. As such, the SCCS has considered that the information available at present is insufficient to allow drawing conclusions on the safety of colloidal silver materials included in this Opinion.

A lot of information is also available in the published scientific literature, and the Applicants are referred to consider the information that may be relevant to safety assessment of their materials.

4. CONCLUSION

1. *In view of above, and taken into account the scientific data provided, the SCCS is requested to give its opinion on the safety of the nanomaterial Colloidal Silver when used in cosmetics including toothpastes and skin care products with a maximum concentration limit of 1%, taking into account the reasonably foreseeable exposure conditions.*

Only a limited amount of data was provided by the Applicants that corresponded to the SCCS Guidance on Safety Assessment of Nanomaterials in Cosmetics (SCCS 1484/12). The provided data were also not in line with the SCCS Memorandum on Relevance, Adequacy and Quality of Data in Safety Dossiers on Nanomaterials (SCCS/1524/13). Although other information is available in open literature relating to the toxicity of nano silver, their relevance with respect to the materials in this submission has not been considered by the Applicants. Due to a number of major data gaps, the SCCS is not in the position to draw a conclusion on the safety of colloidal silver in nano form when used in oral and dermal cosmetic products.

2. *SCCS is requested to address any further scientific concerns with regard to the use of Colloidal Silver in nano form in cosmetic products.*

In addition to the safety assessment of colloidal silver in nano form, consideration should also be given to the likely presence of ionic silver in different types of final products.

5. MINORITY OPINION

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7. ABBREVIATIONS AND GLOSSARY OF TERMS

AAS	Atomic absorption spectroscopy
ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, Excretion
AFM	Atomic force microscopy
AgNPs	Silver nanoparticles
BET	Brunauer Emmett and Teller method based on nitrogen gas absorption
CAS	A chemical registry system established by the Chemical Abstracts Service (CAS)
Colipa	European Cosmetics Association (formerly the European Cosmetic Toiletry and Perfumery Association). Now Cosmetics Europe
Colloidal silver	Colloidal dispersion of silver particles in water
DLS	Dynamic light scattering
ECVAM	European Centre for the Validation of Alternative Methods
EDX	Energy Dispersive X-ray
EFSA	European Food Safety Authority
FTIR	Fourier transform infrared spectroscopy
GC/LC-MS	Gas Chromatography/ Liquid Chromatography coupled with Mass Spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
In vitro test method	Biological method that uses organs, tissue sections and tissue cultures, isolated cells and their cultures, cell lines and subcellular fractions, or non-biological method that uses chemical interaction studies, receptor binding studies, etc [Rogiers and Beken 2000]
IARCC	International Agency on Research of Cancer
ISO	International Organization for Standardization
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
Nanomaterial	An insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm [Regulation (EC) No 1223/2009]
Nanoparticle	A nano-object with all three external dimensions in the nanoscale [ISO/TS 27687:2008, Nanotechnologies - Terminology and definitions for nano]
NRU	Neutral Red Uptake cytotoxicity test
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
SAD pattern	Selected area diffraction pattern
SEM	Scanning electron microscopy
SMPS	Scanning mobility particle sizer
Solubility	The terms 'solubility' and 'persistence' are often used to describe the rate of "degradation". As such there are a number of definitions of solubility (see SCENIHR Opinion 'Scientific Basis for the Definition of the Term "Nanomaterial", 8 December 2010). Solubility in the context of this guidance means disintegration of a nanomaterial in an aqueous medium or biological environment into molecular components with the loss of nano features
Systemic effects	Systemic effect refers to an adverse health effect that takes place at a location distant from the body's initial point of contact and presupposes absorption has taken place
TDS meter	Total dissolved solids meter
TEM	Transmission electron microscopy
UV-Vis	Ultraviolet-visible spectrophotometry
VSSA	Volume specific surface area (see Kreyling et al., 2010)

Annex: Summary of material characterisation data on colloidal silver provided by Applicants in the Opinion

Table 1: Comparison of information on material characterisation provided for Nanosilver in this submission with requirements as given in the SCCS Checklists for Applicants submitting dossiers on Cosmetic Ingredients to be evaluated by the SCCS (SCCS/1588/17)

Information required ^(a)	A, B, C, D, J, K, L	E	F	G	H	I
Chemical identity	Y	Y	Y	Y	Y	Y
Chemical composition	Y/N	Y/N	N	N	N	Y
Particle size ^(b)	Y	N	Y	Y	N	Y
Morphology	Y	N	N	N	N	Y
Surface Characteristics	N	N	N	Y	N	N
Solubility	Y/N	N	N	N	N	Y/N
Surface area	Y	N	N	Y	N	N
Catalytic Activity	N	N	N	N	N	Y
Concentration ^(c)	Y	N	Y	N	Y	Y
Dustiness ^(c)	N	N	N	N	N	N
Density and pour density ^(d)	Y	N	N	N	N	Y
Redox potential	N	N	N	N	N	N
pH ^(e)	Y	N	N	N	Y	Y
Viscosity ^(f)	Y	N	N	N	N	N
Stability	Y*	Y*	Y*	Y*	Y*	Y*
UV absorption	N	N	N	N	N	Y
Other	N	N	N	N	N	N

Y = yes, N = no, Y/N = partly

*: Only stability of the finished product is provided

(a) For details on these parameters see Table 1 of SCCS/1484/12;

(b) For any spray products, size distribution of the droplets as well as of the dried residual particles should be provided;

(c) For dry powder products only;

(d) For granular materials only;

(e) For aqueous solutions;

(f) For liquid dispersions

The Y/N in the abovementioned Table is referring to the **availability of the data** in the submitted files, **not the quality** of the submitted data.

Table 2a: Comparison of Toxicological information provided on Nanosilver in this submission with requirements as given in the SCCS Checklists for Applicants submitting dossiers on Cosmetic Ingredients to be evaluated by the SCCS (SCCS/1588/17)

Information required	Reference	A, B, C, D	E	F	G	H	I
Likelihood and extent of internal exposure via skin, lung, or oral route considering the use type	Section 3-4.1 of SCCS/1564/15	N	N	N	N	N	N
Dermal absorption – for dermally applied products	SCCS/1358/10	N	N	N	N	N	N
Biokinetic behavior, aggregation/ agglomeration considered during tests?	Section 3-4.1 of SCCS/1564/15	N	N	N	N	N	N
Acute Toxicity	Section 3-4.2 of SCCS/1564/15	Y, oral	N	Y, oral	Y, oral, dermal	Y, oral	N
Irritation and Corrosivity	Section 3-4.3 of SCCS/1564/15	Y, skin, eye	N	Y, skin, eye	Y, skin, eye	Y, eye	N
Skin Sensitisation	Section 3-4.4 of SCCS/1564/15	Y	Y	Y	N	N	Y
Mutagenicity/ Genotoxicity ^(a)	Section 3-4.7 of SCCS/1564/15	Y	N	N	Y, bacteria	N	N
Repeated dose toxicity	Section 3-4.5 of SCCS/1564/15	N	N	N	N	N	N
Phototoxicity - for products intended for use in sunlight exposed skin	Section 3-4.9 of SCCS/1564/15	N	N	N	N	N	N
Human data	Section 3-4.10 of SCCS/1564/15 and SCCNFP/0633/02	Y, skin sensitisation				Y, skin sensitisation	Y, skin sensitisation
Reproductive Toxicity ^(b)	Section 3-4.6 of SCCS/1564/15	N	N	N	N	N	N
Carcinogenicity ^(c)	Section 3-4.8 of SCCS/1564/15	Y	Y	N	N	N	N
Other relevant information		N	N	N	N	N	N

Y = yes

N = no

Y/N = partly

NB: for all toxicological data in this Table: these are statements without **any** experimental evidence

a) The Ames test is not considered appropriate for nanomaterial mutagenicity assessment. The following scheme based on in vitro assays is proposed (SCCS/1564/15).

Opinion on Colloidal Silver (nano)

1. Mammalian cell chromosome aberration/clastogenicity – determined either by in vitro chromosome aberration test or micronucleus test. The micronucleus test can be performed by the mononucleate or cytokinesis blocked protocols. In the cytokinesis blocked micronucleus assay, co-exposure to both cytochalasin B and the test nanomaterial for the duration of the experiment is not considered acceptable.
2. An in vitro mammalian cell gene mutation test (e.g. hprt, tk or xprt tests). Other indicator tests, such as the Comet assay, may be included as a further weight of evidence. New in vitro approaches such as cell transformation assays or toxicogenomic approaches may also be useful for identification of genotoxic as well as non-genotoxic carcinogen nanomaterials.
3. In vitro genotoxicity studies should be accompanied by an assessment of cellular and nuclear uptake to demonstrate target exposure to enable a complete evaluation of data-outputs.

^(b) Where point 1 and 2 indicate significant systemic uptake

^(c) Where point 1 and 2 indicate significant systemic uptake and/or bioaccumulation

Table 2B: Summary of toxicological data provided in the submission

Type	Ref	Phys-chem data	Acute	Repeated dose	Genotox bact	Genotox other	Cancer	Repro tox	Irritation	Sensitisation	Adsorption	Kinetics
A, B, C, D, J, K, L	1-12	++ * (11/17)**	Yes, oral	X	X	Yes	Yes	X	Yes, skin, eye	Yes	X	X
E	13-15	+ (3/17)	X	X	X	X	Yes	X	X	Yes	X	X
F	16-18	+ (4/17)	Yes, oral	X	X	X	X	X	Yes, skin, eye	Yes	X	X
G	19-21	+ (5/17)	Yes, oral, dermal	X	Yes	X	X	X	Yes, skin, eye	X	X	X
H	22-24	+ (4/17)	Yes, oral	X	X	X	X	X	Yes, eye	X	X	X
I	25-27	++ (11/17)	X	X	X	X	X	X	X	Yes	X	X

*: +, ++, +++ is available

** : number of parameters available (total is 17)

X: study/ data not available, not provided

NB: For all toxicological data in the Table: these are statements without **any** experimental evidence.

Table 3: Comparison of Exposure information provided for nanosilver in this submission with requirements as given in the SCCS Checklists for Applicants submitting dossiers on Cosmetic Ingredients to be evaluated by the SCCS (SCCS/1588/17).

Information required ^(a)	Provided?
Category of cosmetic products in which the ingredient is intended for use	Y
Concentration of the ingredient in the finished cosmetic product	N
Quantity of the product used at each application	Y (only H)
Frequency of use	Y (only H)
Total area of skin contact	Y (only H)
Duration of exposure	N
Foreseeable misuse which may increase exposure	N
Consumer target groups (e.g., children, people with sensitive, damaged or compromised skin) where specifically required	N
Quantity likely to enter the body (fraction absorbed) for each target group	N
Application on skin areas exposed to sunlight	Y
Estimated dermal exposure based on the intended use of the product	Y
Estimated oral exposure based on the intended use of the product	N
Estimated inhalation exposure based on the intended use of the product	N
Exposure calculation for each target group	N
Other relevant information	N

Y = yes

N = no

Y/N = partly

(a) In the absence of information, the SCCS may use default values for some of the parameters (SCCS Notes of Guidance SCCS/1564/15)