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Safety and bioavailability of silver hydrosol as a source of silver added for nutritional purposes to food supplements

EFSA Panel on Food Additives and Nutrient Sources added to Food (EFSA ANS Panel), Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Metka Filipič, Maria Jose Frutos, Pierre Galtier, Ursula Gundert-Remy, Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright, Paul Tobback, Ana Maria Rincon, Camilla Smeraldi and David Gott

Abstract

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) provides a scientific opinion on the safety and bioavailability of silver hydrosol as a source of silver added for nutritional purposes to food supplements. Silver hydrosol is a suspension comprised of a mixture of positively charged silver ions and silver metal particles in water. The study report submitted, being a gastric disappearance study performed in six individuals, did not provide information on the systemic absorption of silver as such, and was not able to provide information on the bioavailability of silver from silver hydrosol. If silver from silver hydrosol is systematically available a complete toxicological evaluation is needed for its assessment. The application dossier was limited to an acute toxicity study with silver hydrosol and references to toxicological studies performed with forms of silver (e.g. salts of silver) which were considered neither relevant nor adequate to the risk assessment of silver hydrosol. The Panel concluded that the submitted data are insufficient to characterise the silver hydrosol regarding its nano specific properties and to assess either the bioavailability of silver from the source or the safety of the silver hydrosol as a source of silver added for nutritional purposes to food supplements.

Keywords: silver hydrosol, silver, food supplements

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Correspondence: fip@efsa.europa.eu

Panel members: Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright and Maged Younes.

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Summary

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety and bioavailability of silver hydrosol as a source of silver added for nutritional purposes to food supplements.

The current assessment by the Panel is based on the information submitted in the application dossier and the additional information provided by the applicant following a request by EFSA.

According to the applicant, silver hydrosol is a suspension comprised of a mixture of positively charged silver ions and silver metal particles in USP23 grade water, with a total silver concentration in the range of 10–27.5 μg/mL. Information on the particle size analysis (particle size and size distribution) performed by transmission electron microscopy (TEM) and atomic force microscopy (AFM) showed that the material is in the nano range. No full characterisation of the nanomaterial according to the EFSA Guidance for risk assessment of engineered nanomaterials (EFSA Scientific Committee, 2011) was provided and in the absence of full characterisation, it was not possible to ascertain which nano specific properties require data for evaluation.

A study report showed that the absorption of silver from silver hydrosol is in the order of 53% of the amount orally administered. The Panel noted that this study, being a gastric disappearance study performed in six individuals, did not provide information on the systemic absorption of silver as such, and was not able to provide information on the bioavailability of silver from silver hydrosol.

The Panel noted that if silver from silver hydrosol was systemically available, this would require a complete toxicological evaluation. Therefore, toxicological studies with silver hydrosol were requested by EFSA but not provided by the applicant.

The application dossier was limited to an acute toxicity study with silver hydrosol and references to toxicological studies performed with forms of silver (e.g. salts of silver) which were considered neither relevant nor adequate to the risk assessment of silver hydrosol. The Panel further noted that the lack of adequate characterisation of the silver hydrosol and the material in the published studies not only precluded extrapolation of the data (read across) but also an evaluation of the relevance of the submitted publications.

The Panel concluded that the submitted data are insufficient to characterise the silver hydrosol regarding its nano specific properties and to assess either the bioavailability of silver from the source or the safety of the silver hydrosol as a source of silver added for nutritional purposes to food supplements.

Table of contents

1. Introduction

The present scientific opinion deals with the evaluation of the safety and bioavailability of silver hydrosol as a source of silver added for nutritional purposes to food supplements.

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background

The European Union legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of silver hydrosol as a source of silver added for nutritional purposes to food supplements. The relevant Union legislative measure is:

- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements.[1]

1.1.2. Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[2], the European Commission (EC) asks the European Food Safety Authority (EFSA) to provide a scientific opinion, based on its consideration of the safety and bioavailability of silver hydrosol as a source of silver added for nutritional purposes to food supplements.

1.2. Interpretation of the Terms of Reference

The Panel is aware that silver is not included in the positive lists of minerals and vitamins that can be added to food supplements, as defined by Annex I to Directive 2002/46/EC, respectively. It is not in the remit of this Panel to establish whether silver should be added to the list of minerals and vitamins permitted for use in the manufacture of food supplements for nutritional purposes.

1.2.1. Information on existing evaluations and authorisations

A few references related to previous assessments of silver, as salt or metallic silver, were submitted in the applications dossier (JECFA, 1977; ATSDR, 1990; EPA, 1991).

In 2008, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) evaluated the safety of silver hydrosol added for nutritional purposes as a source of silver in food supplements and on bioavailability of silver from this source and concluded that due to the lack of an appropriate dossier supporting the use of silver hydrosol, the safety of silver hydrosol and the bioavailability of silver from silver hydrosol could not be assessed (EFSA ANS Panel, 2008).

The ANS Panel re-evaluated the safety of silver (E 174) as a food additive and concluded that the information available was insufficient to assess the safety of silver as a food additive (EFSA ANS Panel, 2016).

2. Data and methodologies

2.1. Data

The present evaluation is based on the data on silver hydrosol in a newly submitted dossier by the applicant (Documentation provided to EFSA n.1) and additional information submitted by the applicant during the assessment process in response to a request by EFSA (Documentation provided to EFSA n.2).

[1] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

[2] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing Guidance from the EFSA Scientific Committee.

The ANS Panel assessed the safety of silver hydrosol as a proposed source of silver for use in food supplements in line with the principles laid down in the 'Guidance on submissions for safety evaluation of nutrients or of other ingredients proposed for use in the manufacture of foods' (SCF, 2001a). However, the Panel considered that to reflect state of the art scientific knowledge and welfare considerations the reference to the 'Guidance on submissions for food additive evaluations by the Scientific Committee on Food' (SCF, 2001b) should be replaced by the latest existing guidance on the safety evaluation of food additives, namely the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

With respect to the evaluation of bioavailability of silver from the proposed source silver hydrosol, the principles contained in the 'Guidance on submissions for safety evaluation of nutrients or of other ingredients proposed for use in the manufacture of foods' (SCF, 2001a) were followed.

Dietary exposure to the nutrient source was estimated based on the proposed uses and use levels, which in the current application, was limited to food supplements.

In its initial assessment, the Panel noted that the proposed source silver hydrosol would require additional parameters for characterisation because it would appear to fall in the nano range. The applicant was therefore requested to characterise the material in accordance with the principles and data required by the EFSA Guidance for risk assessment of engineered nanomaterials (EFSA Scientific Committee, 2011).

3. Assessment

3.1. Technical data

3.1.1. Identity of the substance

According to the applicant, silver hydrosol is a mixture of positively charged silver ions and silver metal particles in USP23 grade water, with a total silver concentration in the range of 10–27.5 μg/mL. Silver in silver hydrosol is present in different oxidation states, including the zerovalent metal state (Ag^0) and the +1 cation state (Ag^+). The applicant stated that in this form, silver should be differentiated from uncharged elemental silver (Ag^0) or silver ions (Ag^+) present in solution following their dissolution in a solvent.

In the application dossier, CAS No 1191942-51-4 was proposed as Registry CAS Number for silver hydrosol. The Panel noted that this CAS number refers to 'Silver, ion (Ag_{14}^{1+}), hydrate (1:34)' (SciFinder, software).

Metallic silver (Ag^0) is insoluble in water, while silver ions can be soluble. According to the applicant, the surface of silver metal can be slowly oxidised by dissolved oxygen in water. This creates a layer of silver oxide on the surface, which is slightly soluble and can release silver cations into the solution. The concentration of soluble silver ions remaining in solution depend upon the concentration and type of negatively charged anions present in the solution. Furthermore, depending on the solution environment, the silver ions can be reduced back into silver metal atoms. Exposure to light can facilitate the cycling of silver oxidation states, either oxidised or reduced.

Silver hydrosol is supplied in two preparations depending on the concentration on silver: 10 and 23 μg Ag/mL silver hydrosol (measured by atomic-absorption spectroscopy (AAS) or inductively coupled plasma mass spectrometry (ICP-MS)).

Information on the particle size analysis (particle size and size distribution) performed by transmission electron microscopy (TEM) and atomic force microscopy (AFM) was submitted (Documentation provided to EFSA n.1 and 2). The same samples were analysed with both methodologies and a summary of the results are presented in Table 1.

Table 1: Summary of the data on particles analysis of nine silver hydrosol samples as provided by the applicant (Documentation provided to EFSA n. 1 and 2)

Method of analysis	Range of average particle diameter of individual samples (nm)	Combined average particle diameter of all samples (nm)
Transmission electron microscopy (TEM)	1.8–4.5	3.3[(a)]
Atomic force microscopy (AFM)		Minimum particle height: 0.86 Maximum particle height: 5.95

(a): Average of 60722 particles measured.

Aggregation and agglomeration was not observed.

No information on specific surface area was provided in the application dossier. Regarding the surface chemistry, the applicant stated that there are only two ingredients in the formulation, high purity water (USP23 grade water) and 99.999% pure silver. No ingredients are added to the formulation of silver hydrosol that could potentially modify the surface reactivity or add new functionality (Documentation provided to EFSA n.2).

Zeta potential measurements could not be performed on either 10 or 23 μg/mL silver hydrosol (Documentation provided to EFSA n.2).

3.1.2. Proposed specifications

No chemical and microbiological specifications for the source, in a modelled on recent EU or other international accepted format were provided.

The applicant has provided the results of analysis of five non-consecutive, independent batches on microbiological parameters, toxic elements (Cd, Cr, Hg, As, Pb), major carbamates-PCBs, major organophosphorus and organochlorine pesticides (Documentation provided to EFSA n.2).

3.1.3. Manufacturing process

The suspension of silver hydrosol is produced from silver electrodes (purity ≥ 99.999%) by electrolysis, which creates a mixture of positively charged silver ions and particles of silver, suspended in USP23 grade water (Documentation provided to EFSA n.1).

3.1.4. Methods of analysis in food

According to the applicant, silver content is analysed by AAS and ICP-MS (Documentation provided to EFSA n.1).

3.1.5. Stability of the substance and reaction and fate in food

The applicant provided stability data of six commercial samples of silver hydrosol after 3 years of storage in amber glass bottle. The Panel noted that the stability of silver hydrosol was evaluated only in terms of the silver content (Documentation provided to EFSA n.1).

3.2. Proposed uses and use levels

According to the applicant, silver hydrosol is proposed for use in two different formulations, providing 10 μg Ag/mL of silver hydrosol (Sovereign Silver®) and 23 μg Ag/mL of silver hydrosol (Argentyn23®).

The recommended maximum daily dosage intake for adults is seven doses of 5 mL each for Sovereign Silver®, and three doses of 5 mL each for Argentyn23®; therefore, the maximum total supplemental intake 5 μg Ag/kg body weight (bw) per day, corresponding to 350 μg Ag/day for a 70-kg adult. The Panel noted the maximum total supplemental intake of 5 μg Ag/kg bw per day proposed by the applicant is equal to the oral reference dose (RfD) (EPA, 1991).

3.3. Biological and toxicological data

3.3.1. Bioavailability

A report of a bioavailability study with silver hydrosol under evaluation was submitted (Documentation provided to EFSA n.1). Six (3 M/3 F) healthy volunteer adult Caucasian (ages 30–54)

were given an oral dose of 50 μg silver hydrosol. A nasogastric tube was introduced to each subject. Samples of ingested fluids were reacquired through a nasogastric tube pump in order to measure via AAS how much silver had been absorbed by the mucosal surfaces from the mouth to the level of the empty stomach at specific intervals.

This study showed that the silver absorption from silver hydrosol was in the order of 53% of the amount orally administered which is equivalent to the typical recommended dosage. However, according to the applicant the amount of silver absorbed will depend on the characteristics of the 'individual's body fluids', the timing of administration and fasting conditions (bioavailability will be greater when the stomach is empty). The Panel noted that this study, being a disappearance study, did not provide information on the systemic absorption of silver as such, and was not able to provide information on the bioavailability of silver from silver hydrosol.

3.3.2. Toxicity data

An acute oral toxicity study in rats with Argentyn 23® was submitted within the application dossier Documentation provided to EFSA n.1). Five adult male and female Crl:CD(SD)IGS BR rats were administered a single dose (based on dose volume of 20 mL/kg) by oral gavage and observed at approximately 1, 2.5 and 3 h after dose administration and once daily thereafter for at least 14 days. All the animals survived until the scheduled sacrifice and gained weight throughout the study. At necropsy, according to the authors, discoloured-dark liver lobes in one male and one female were possible treatment-related but considered inconclusive because no microscopic evaluation was performed. The remaining finding, soft heart in one male was considered incidental. No visible lesions were noted in the remaining animals.

No additional toxicity data on silver hydrosol were submitted as part of this application. The dossier included references to publications on conventional forms of silver, which were considered neither relevant nor adequate to the risk assessment of silver hydrosol. The Panel further noted that the lack of adequate characterisation of the silver hydrosol and the material in the published studies not only precluded extrapolation of the data (read across) but also an evaluation of the relevance of the submitted publications.

3.4. Discussion

The current assessment by the Panel is based on the information submitted in the application dossier (Documentation provided to EFSA n.1) and the additional information provided by the applicant following a request by EFSA (Documentation provided to EFSA n.2).

According to the applicant, silver hydrosol is a suspension comprised of a mixture of positively charged silver ions and silver metal particles in USP23 grade water, with a total silver concentration in the range of 10–27.5 μg/mL.

Information on the particle size analysis (particle size and size distribution) performed by TEM and AFM showed that the material is in the nano range. No full characterisation of the nanomaterial according to the EFSA Guidance for risk assessment of engineered nanomaterials (EFSA Scientific Committee, 2011) was provided and in the absence of full characterisation, it is therefore not possible to ascertain which nano specific properties require data for evaluation.

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The Panel noted that if silver from silver hydrosol was systemically available, this would require a complete toxicological evaluation. Therefore, toxicological studies with silver hydrosol were requested by EFSA but not provided by the applicant.

The application dossier was limited to an acute toxicity study with silver hydrosol and references to toxicological studies performed with forms of silver (e.g. salts of silver) which were considered neither relevant nor adequate to the risk assessment of silver hydrosol. The Panel further noted that the lack of adequate characterisation of the silver hydrosol and the material in the published studies not only precluded extrapolation of the data (read across) but also an evaluation of the relevance of the submitted publications.

4. Conclusions

The Panel concluded that the submitted data are insufficient to characterise the silver hydrosol regarding its nano specific properties and to assess either the bioavailability of silver from the source or the safety of the silver hydrosol as a source of silver added for nutritional purposes to food supplements.

Documentation provided to EFSA

1) Dossier 'Silver hydrosol proposed for addition to Annex II of Base EC Directive 2002/46/EC on food supplements'. Submission on 17 March 2016. Missing information submitted on 23 May 2016.
2) Additional information. 17 December 2017; 3 January 2018. Submitted by Natural Immunogenics Corp in response to a request from EFSA.

References

ATSDR (Agency for Toxic Substances and Disease Registry), 1990. Toxicological profile for silver. Available online: https://www.atsdr.cdc.gov/ToxProfiles/tp146.pdf

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2008. Scientific Statement of the Panel on Food Additives and Nutrient Sources added to Food on a request from the Commission on Silver hydrosol as a source of silver added for nutritional purposes to food supplements. EFSA Journal 2008;6 (12):884, 3 pp. https://doi.org/10.2903/2fj.efsa.2008.884

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2012. Guidance for submission for food additive evaluations. EFSA Journal 2012;10(7):2760, 60 pp. https://doi.org/10.2903/j.efsa.2012.2760

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2016. Scientific opinion on the re-evaluation of silver (E 174) as food additive. EFSA Journal 2016;14(1):4364, 64 pp. https://doi.org/10.2903/j.efsa.2016.4364

EFSA Scientific Committee, 2009. Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: general Principles. EFSA Journal 2009;7(7):1051, 22 pp. https://doi.org/10.2903/j.efsa.2009.1051

EFSA Scientific Committee, 2011. Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain. EFSA Journal 2011;9(5):2140, 36 pp. https://doi.org/10.2903/j.efsa.2011.2140

EPA (Environmental Protection Agency), 1991. Silver; CASRN 7440-22-4. Available online: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0099_summary.pdf

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1977. Summary of toxicological data of certain food additives. WHO Food Additives Series No. 12. Silver.

SCF (Scientific Committee on Food), 2001a. Guidance on submissions for safety evaluation of nutrients or of other ingredients proposed for use in the manufacture of foods. Opinion expressed on 11 July 2001.

SCF (Scientific Committee for Food), 2001b. Guidance on submissions for food additive evaluations by the Scientific Committee on Food. SCF/CS/ADD/GEN/26 Final. 12 July 2001.

Abbreviations

AAS	atomic-absorption spectroscopy
AFM	atomic force microscopy
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
ATSDR	Agency for Toxic Substances and Disease Registry
Bw	body weight
CAS	Chemical Abstracts Service
EPA	Environmental Protection Agency
ICP	inductively coupled plasma mass spectrometry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MS	mass spectrometry
PCB	polychlorinated biphenyl
RfD	reference dose
SCF	Scientific Committee on Food
TEM	transmission electron microscopy
WHO	World Health Organization